Title: Ayahuasca, Mental Health, and Behavioral Change: A Field Experiment in Brazil
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Project Overview
We are collaborating with a large (legal) ayahuasca center in Brazil to use field experiments to study the effects of ayahuasca on mental health and behavioural change in Brazil. Our work has already delivered the first large-scale RCT on the effects of psychedelics outside of clinical settings, and more generally, the largest ever RCT on the effects of psychedelics in any setting.

We build on a growing body of experimental and non-experimental work documenting transformative positive effects of psychedelics on mental disorders (Griffiths et al. 2016, Dos Santos et al. 2016, Carhart-Harris et al. 2021, Mitchell et al. 2021), addiction recovery (Johnson et al. 2017), and prosociality, mood and spirituality (Griffiths et al. 2006, Griffiths et al. 2018). We complement this work by studying the effects of psychedelics outside the clinic, with a much more cost-effective means of delivery (group-based during a one-off ceremony, rather than one-to-one, with many hours of therapy per participant). In addition, with a sample size many times larger than clinical studies, we have statistical power to detect effects on outcomes less directly impacted (e.g. savings, labour market effects).

Our core experiment design sees first-time ayahuasca takers randomly assigned to receive a placebo or ayahuasca, upon showing up to their assigned ayahuasca ceremony. We then send follow-up surveys to these participants three days, six weeks, and six months later. We also send follow-up surveys to the participants that did not show up to their assigned ceremony. While non-attendance was not randomized, we can use diff-in-diff to estimate suggestive effects of attending the ceremony and taking the placebo relative to not attending at all.

We have one completed paper that has come out of our work so far: “Ayahuasca Without Therapy Durably Improves Well-Being.” We have appended this paper, in case the extra details would be useful. We have not posted the paper publicly yet, though it is under review at *Nature*. The results of that paper are best summarized by its abstract:

We partnered with an ayahuasca center in Brazil to run the largest ever randomized controlled trial of psychedelics. The one-time ayahuasca treatment is delivered in a ritualized group setting, and without accompanying therapy, making it low-cost. Relative to placebo, ayahuasca increases happiness and reduces psychological distress six months later by roughly 0.4 standard deviations. These effects are almost entirely driven by participants that were distressed at baseline. Improvements in well-being are strongly positively correlated with the self-reported mystical nature of trips. We estimate the mental health benefits of participating in an ayahuasca ceremony to be roughly 200 times the cost of 24 USD. Our findings demonstrate the effectiveness of a low-cost scalable form of psychedelic treatment.

We note that the last two sentences of that abstract speak directly to the NBER’s call for “projects that propose to test scalable interventions with the potential to broadly improve population health.” The single most important asset of our collaboration is that we are shedding light on the effects of low-cost psychedelic treatment – in stark contrast to existing

clinical trials on psychedelics, where treatment is expensive, largely because of the focus on psychedelics being accompanied by one-to-one psychotherapy.

In addition to our results on well-being, we have also collected economic outcomes (for a full description, see our pre-registration here). We plan to write a second paper on the economic effects of ayahuasca, though we have limited power to detect effects with the sample we have so far.

Proposed Activities

While we have the ongoing support of our partner center, along with ethics approval from UBC, we have ceased recruitment, as we have run out of funding. We thus seek funding from NBER to begin a new set of experimental sessions, that would broadly aim to achieve the following:

1. A full clinical trial replication of the well-being results explored in the paper we describe above, though with clinically-validated measures of depression (PHQ-9) and anxiety (GAD-7) (we previously used the Kessler-10 scale of psychological distress).

2. Collection of a broad set of economic, decision-making, and behavioural change-related outcomes (measured in Qualtrics follow-up surveys), to properly explore possible mechanisms for enduring effects on well-being, along with possible downstream effects of well-being improvements on economic outcomes. Given the Brazilian context, we can link participants with administrative labor market data using their RAIS ID (in the data we have collected so far, the vast majority of participants consent to such a linking).

3. A key conjectured mechanism for psychedelics' effects is some form of neuroplasticity. The aspect of neuroplasticity conjectured to be most profoundly affected, and to help in treatment of depressive symptoms, is social neuroplasticity. To get at this, we will utilize tests measuring social cognition such as Reading the Mind in the Eyes Tests (RMET; Baron-Cohen, et. al 2001). We hypothesize that if the temporary social neuroplasticity improvements detected by Dölen and collaborators in mice (see "Psychedelics reopen the social reward learning critical period", *Nature* 2023) are also present in human subjects, participants in treatment groups will be more responsive to online training in reading emotion for an interval of days following treatment sessions. Our multiple follow-up surveys will allow us to estimate the precise duration of any such neuroplasticity openings.

We recognize that our application might be unusual in the sense that we have already run experimental sessions. But we are open and flexible to accommodate exactly the requirements for an NIH clinical trial – for example, we expect that this will require the NIH-funded trial to be done from scratch, with only new recruits, and with write-ups excluding any data we have already collected.

Anticipated Budget Needs

We have a good sense of costs given that we have already run experimental sessions. The cost per experimental session is around $5k, with this cost covering participant incentives for the session and the three follow-up surveys (3-day, 6-week, 6-month), along with salary for

one research assistant, and to cover the cost of the center's staff time. A single session has roughly 50 participants that show up (randomly assigned to ayahuasca or placebo), and 25 that do not show up (non-randomly assigned, but still surveyed to be able to do the diff-in-diff analysis).

We anticipate running 15 new experimental sessions over the course of the 12 to 18 months following funding access, costing $5k*15 = $75k. This would deliver a sample of 750, randomly assigned to ayahuasca or placebo. Beyond this, $10k would cover field visits and accommodation for the three PIs. This $85k funding alone would allow us to run a basic version of the clinical study.

Beyond the basic study, we would need additional funding for the more "bells-and-whistles" study, including:

- A fourth follow-up survey, 1-2 years after the ceremony @ $1.1k for 15 sessions = $16,500
- In-person lab experiment incentives @ $40/person for 600 people = $30,000
- Graduate student RA support @ $25/hour for 10 hours per week for 12 months = $13,000
- GRAND TOTAL = $147,500

Preliminary Power Calculations
With N = 750 and predictive baseline measures of outcomes, and a test size of 5%, we will have 80% power to detect effects of 0.24 SD. For effects on well-being, we note that in our completed paper, we reject the null of no effect even with a sample much smaller than 750, because the well-being effects are so large (around 0.4 SD).

Ayahuasca Without Therapy Durably Improves Well-Being

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Abstract

We partnered with an ayahuasca center in Brazil to run the largest ever randomized controlled trial of psychedelics. The one-time ayahuasca treatment is delivered in a ritualized group setting, and without accompanying therapy, making it low-cost. Relative to placebo, ayahuasca increases happiness and reduces psychological distress six months later by roughly 0.4 standard deviations. These effects are almost entirely driven by participants that were distressed at baseline. Improvements in well-being are strongly positively correlated with the self-reported mystical nature of trips. We estimate the mental health benefits of participating in an ayahuasca ceremony to be roughly 200 times the cost of 24 USD. Our findings demonstrate the effectiveness of a low-cost scalable form of psychedelic treatment.

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1 Introduction

Recent clinical trials report transformative effects of psychedelic-assisted therapy on depression, post-traumatic stress disorder, and other mental health conditions *(1–6)*. These results have the potential to reshape mental health treatment *(7)*, particularly for anxiety and depressive disorders, which affect around half a billion individuals globally *(8)*. Yet the practical lessons of existing trials have been questioned due to their small samples, lack of long-term follow-up, insufficient reporting on functional unblinding, lack of pure control groups, non-diverse participant pools, and participants with prior experience taking psychedelics *(9–13)*.

An additional concern arises from the bundling of psychotherapy with psychedelic drugs, with this concern contributing to the rejection of MDMA-assisted treatment for post-traumatic stress disorder by the FDA *(14)*. Adding therapy makes it impossible to measure causal effects of psychedelics in therapy's absence. And its absence is, by some way, the most common means of ingesting psychedelics—as in the use of psychedelics in traditional and indigenous ceremonies, and at mass gatherings *(15, 16)*. Furthermore, clinical trials typically involve conservative screening criteria, high degrees of clinical control, and are limited to participants suffering acute physical or psychological conditions *(17)*. These aspects make the cost of administering psychedelics in clinical studies high *(18)*, and render sample sizes small. They also limit external validity given that most of these features are absent in more naturalistic and traditional settings where the vast majority of psychedelic substances are ingested.

In Brazil, Peru, Bolivia, Uruguay, and the Netherlands, psychedelics are available legally, and consumed by millions *(19)*. These settings have the potential to answer whether transformative effects in the clinic translate to informal settings where distribution is typically low cost, without clinical oversight, and without therapeutic accompaniment. To explore this, we partnered with a large ayahuasca center in Brazil, where ayahuasca—a traditional psychoactive tea—is legally available for ritualistic use. The center recruited 429 participants for a single-blind randomized assignment to ayahuasca or a placebo, in the context of group ceremonies with no accompanying psychotherapy. This experiment represents the largest randomized controlled trial (RCT) of psychedelics yet run,[1] and the first large-N placebo-controlled experiment on psychedelics without accompanying psychotherapy.

The size and statistical power advantage of undertaking RCTs outside of the clinic comes at the cost of relinquishing aspects of experimental control *(20)*. In particular, though the re-

[1]Two hundred and fifty-two participants were randomized to ayahuasca or placebo and took part in a ceremony. We also survey the 144 participants that did not attend their assigned ceremony, and the 33 participants that attended a ceremony in which all were given ayahuasca. The largest psychedelic trial before ours randomized 233 participants to either a 1mg, 10mg, or 25mg dose of psilocybin *(4)*.

searcher may randomize assignment to treatment, in practice, actual assignment is conducted by the provider, and compliance with the researchers' assignment instructions may not be perfect. To the extent that there is selection in assignment, this would lead to bias that would confound causal inference drawn from the RCT. Fortunately, this problem is common in the social sciences, and we apply well-known statistical corrections for imperfect assignment in our analysis.

2 Experiment design

Recruitment and randomization. The center recruited participants following its status quo protocols that include social media, walk-in registrations, and other forms of outreach (full details in materials and methods section A.2). Those who had not taken ayahuasca before were given the option of participating in a study in which they would be randomly assigned to receive either ayahuasca or a placebo—a similar-looking non-psychoactive tea named jurema. We pre-registered the experiment in the AEA RCT registry (ID #10400, we give further details and explain deviations in the supplementary text). Four hundred and twenty-nine participants consented to participate in the study, completed a baseline survey, and were scheduled to one of six group sessions that took place from June 2023 to February 2024 (see CONSORT diagram in fig. 1). All participants are adults living in Brazil—this is not a psychedelic retreat oriented towards foreigners *(21)*.

The center used a random number generator to randomly assign participants to receive ayahuasca or the placebo (jurema), stratifying on session and gender. Two hundred and eighty-five participants attended their assigned ceremony. At the start of each four-hour secular ceremony, the center owners give a brief explanation of the effects of ayahuasca to expect, followed by a short lecture on general life lessons (supplementary text section B.2), with no accompanying therapy otherwise. Participants are given one serving of tea (ayahuasca or jurema; blinded to the participant but not the center), and advised to be silent and to close their eyes throughout the ceremony, in which music is played. A serving of ayahuasca contains 9mg of DMT (N, N-Dimethyltryptamine) per 50ml, with 50ml given to men, and 40ml given to women. A serving of jurema tea also contains DMT, but this DMT is broken down by the stomach enzyme monoamine oxidase (MAO), preventing jurema from having psychoactive effects (ayahuasca differs in that it contains MAO inhibitors; see details in supplementary materials section A.1). Each participant is offered a second, optional, serving of the same substance after two hours.

Follow-up. We sent follow-up surveys to all 429 participants three days, six weeks, and six months after each experimental session. At baseline participants were asked to pledge not to take ayahuasca after their assigned ceremony until after the six-week follow-up survey. At the end of the six-week follow-up survey, we revealed the actual treatment status to each participant.

In each follow-up survey, we elicit self-reports of: psychological distress using the ten-item Kessler scale (scored 0 to 40, cutoff of 15 for moderately or severely distressed), happiness (0 to 6), and to measure deeper notions of well-being, we use the eight-item Flourishing Scale (0 to 32) *(22)*. In the three-day follow-up we ask a range of questions about participants' ceremony experiences. We ask about the meaningfulness of the experience *(23)*, as well as seven items from the Mystical Experience Questionnaire *(24)*, which covers the participant's "feeling that [they] experienced something profoundly sacred and holy," as well as other domains related to the mystical nature of trips (full survey questions are in supplementary materials section A.3).

Follow-up survey response rates are high for those that attended their assigned ceremony, ranging from 88 to 100% per session, though they are lower for no-shows, ranging from 67 to 75% (fig. 1).

Non-compliance and statistical analysis. Due to the non-clinical setting and the randomization protocol being administered by center staff (not the researchers), there is imperfect compliance with treatment assignment. In addition, in the sixth experimental session, an error in distribution led to all participants being given ayahuasca.

For our analysis of the effects of ayahuasca relative to placebo, we use data for the 252 participants that attended the first five sessions, where 90% of those assigned the placebo received the placebo and 83% of those assigned ayahuasca received ayahuasca. We use an intent-to-treat approach—we compare those randomly assigned to ayahuasca with those randomly assigned to placebo, controlling for randomization strata (session-by-gender indicator variables) and the baseline measure of well-being, with robust standard errors (for additional details see supplementary materials section A.4). To adjust for non-compliance, we also report instrumental variable (IV) estimates, in which we use treatment assignment as an IV for treatment received *(25)*.

For our analysis of how trip quality correlates with well-being changes, we use data on the 159 participants that received ayahuasca, including those from the sixth session. For this analysis we regress the *change* in well-being from baseline to follow-up on the participant's mystical experience score, controlling for the baseline measure of well-being, with robust standard errors.

Of the 429 participants, 144 did not attend their assigned ceremony (fig. 1). Since these

no-shows were not randomly assigned to be absent, we use a difference-in-differences analysis to shed light on the well-being effects of attending the ceremony *(26)*. We cluster standard errors at the participant-level. This approach tests for whether the change in well-being from baseline to each follow-up is larger for those that attended the ceremony than for those that did not attend.

3 Results

The 429 participants have an average age of 35. Sixty-two percent are female, 45% are non-white, and 45% practice a religion (table S1). Participants display the full range of psychological well-being at baseline, with 58% being classified as distressed. The median participant falls in an income bracket of BRL 2,001 to 3,000 (363 to 544 USD) per month, where BRL 3,000 is roughly the average monthly earnings in the country in 2023 *(27)*.

Participants randomly assigned to receive ayahuasca have similar characteristics to those randomly assigned to receive the placebo, whether considering the sample that attended the ceremony, or the samples that also completed subsequent follow-up surveys (columns 1 to 4, S2 to S5). One exception is that participants assigned ayahuasca are less happy at baseline (column 1, table S2). This imbalance would bias against finding positive effects of ayahuasca, though in practice, we always control for the baseline well-being measure in our analysis.

Eighty percent of the participants that received ayahuasca opted for the second serving, as did 86% of those that received the placebo. While the experiment is single-blind, there is functional unblinding—participants tend to know what treatment they received—as is common in psychedelic macrodose experiments (see materials and methods section A.6 for details, and for suggestive evidence on the role of placebo effects).

Ayahuasca versus placebo. Participants that take ayahuasca report remarkable experiences in the first follow-up survey three days later: 36% report that the experience was the single most meaningful experience they have ever had, while a further 40% report it to be among their top-five most meaningful experiences. These rates are higher than those reported in seminal clinical trials of psilocybin *(1, 23)*, which may partly be an effect of the ritualized ceremony setting here compared with the clinical setting of those trials. Using treatment assignment as an instrumental variable (IV) for actually receiving ayahuasca, we find that ayahuasca substantially increases reports of mystical experiences, ego dissolution, and meaningfulness, relative to the

placebo condition (table S6).[2] However, ayahuasca also causes more vomiting (5% vs. 67%, using IV estimates), diarrhea (4% vs. 15%), dizziness (9% vs. 36%), and self-reports of "bad" (3% vs. 13%), or "challenging" trips (5% vs. 24%, table S7).

Ayahuasca durably improves well-being (fig. 2). Recipients randomly assigned to ayahuasca experience significant and durable reductions in distress, and improvements in happiness, relative to placebo. Pooling the three follow-up surveys, we estimate statistically significant beneficial effects on distress ($p < 0.01$) and happiness ($p < 0.001$), though we estimate null effects on flourishing ($p = 0.56$). The effects are relatively stable over time, and the IV effects of ayahuasca on distress and happiness are roughly 0.4 standard deviations at the six-month follow-up.

Clinical trials of psychedelics restrict to participants that suffer from mental or physical ill-health. Our sample is broader, and the difference matters: the effects of ayahuasca on well-being are entirely driven by participants classified as distressed at baseline; for whom the six-month effect on distress and happiness is roughly 0.9 standard deviations (fig. 2B). These are large effects which are stable and, if anything, increase over time. This may be due to induced behavioral changes, or to a decay in ceremony-only effects. These effects are comparable to, but more enduring than, effects of single-dose psilocybin relative to placebo in clinical trials with depressed participants *(4, 6, 28)* (these three clinical trials track outcomes up to 12, six, and two weeks, respectively). A Cohen's *d* of 0.9 is also comparable to the effects of cognitive behavioral therapy *(29)*, though the question remains as to whether the effects of ayahuasca are as enduring *(30, 31)* (these RCTs report outcomes multiple years after treatment). In contrast, the only statistically significant effect we find for non-distressed individuals is a positive, but fleeting, effect on happiness (fig. 2C).

Despite the center's lighter screening than clinical trials, we do not see evidence of negative side effects after six months (table S8), while we see immediate positive effects on optimism about future well-being, and if anything, positive (though statistically insignificant) effects on health in general (fig. S2).

Relative to clinical trials in settings in which psychedelics are illegal, we are better placed to assess addiction risk, given that study participants can legally access ayahuasca at our partner center or elsewhere. We see no evidence of ayahuasca being addictive: the fraction that report

[2]The average scores for placebo-takers are low, and with a mass at zero (fig. S1), consistent with participants not experiencing psychedelic trips through taking jurema. For example, the average score of 12/35 on the seven-item Mystical Experience Questionnaire is consistent with participants answering "So slight I cannot decide" or "Slight" to questions like "Please rate the degree to which you experienced... Feelings of universal or infinite love." In contrast, the average score of 24/35 (69%) for participants that took ayahuasca is comparable to the 64% average, though on the 30-item Mystical Experience Questionnaire, for high psilocybin dose participants in a seminal clinical trial for patients with life-threatening cancer *(1)*.

having taken ayahuasca in the six months following the ceremony is only 25%, and not significantly different between those assigned ayahuasca versus jurema ($p = 0.91$, fig. S3). There is some weak evidence of ayahuasca increasing subsequent non-ayahuasca drug use, though with no p-values below 0.09 (fig. S3).

Trip quality and well-being effects. A key question in psychedelic research is whether the subjective features of trips are necessary for therapeutic effects *(32)*. We explore this question by correlating participants' reports of mystical experiences with well-being changes from baseline to follow-up *(1, 2)*, restricting to the participants given ayahuasca.

While the mystical-ness of experiences was not randomly assigned, the intensity of the mystical experience reported is not statistically significantly correlated with baseline distress, happiness, or flourishing (first column, fig. 3). Nevertheless, when correlating mystical experience with well-being changes, we control for the baseline measure of the well-being outcome.

More mystical experiences are associated with greater improvements in well-being. At the three-day follow-up, more mystical experiences predict a larger reduction in distress ($p < 0.01$), a larger increase in happiness ($p < 0.0001$), and even a larger increase in flourishing ($p < 0.001$)—suggesting that our overall null effect on flourishing may mask positive effects for those with the most intense subjective experiences (second column, fig. 3). These correlations are similar at the six-week and six-month follow-ups (third and fourth columns), although they attenuate over time, and two of three are no longer statistically significant after six months (with $p = 0.15, 0.09$, and 0.21). These findings of strong associations between well-being improvements and acute subjective experiences are similar if we use alternative measures of subjective experience, although the correlations at the six-month point become even less robust (table S9).

Participants that report having had challenging ayahuasca trips nevertheless experience greater improvements in well-being than placebo participants (fig. S4), consistent with the view of the center owners that a trip is challenging when a participant is truly working through their problems. Bad trips and the placebo deliver similar changes in well-being (fig. S5). In addition, we do not see a greater prevalence of deteriorating well-being following bad or challenging trips relative to the placebo (figs. S4, S5).

Ceremony effects. By surveying no-shows, we can also shed light on the well-being effects of the ceremony (and placebo), in the absence of the drug. We do so using a difference-in-differences design, valid under a parallel trends assumption—i.e. that in the absence of the ceremony, well-being outcomes would have trended similarly for no-shows and ceremony attenders. We find suggestive evidence of parallel pre-trends in happiness, using the baseline

report of happiness along with a retrospective report of happiness made in the same baseline survey (middle panels, fig. 4). However, participants that decide to go to an ayahuasca ceremony may be those that would attempt to improve their mental health even in the absence of the ceremony, causing the parallel trends assumption to fail. The following results come with this caveat.

We find suggestive evidence of positive well-being effects of attending the ceremony and taking the placebo (fig. 4A). This finding reduces the likelihood that our positive effects of ayahuasca are due to disappointment lowering well-being in the placebo group. We find positive and enduring effects of attending and taking ayahuasca on all three measures of well-being, though the effect on flourishing is statistically insignificant at the six-month point (fig. 4B).

The reductions in distress imply that a single ceremony reduces the effective number of distressed life-years by 0.12 (assuming conservatively that the treatment effect dissipates to zero immediately after we last measure it at six months). Following the approach of Open Philanthropy, we estimate the benefits of a ceremony to amount to $4,608, or 192 times the $24 price of a ceremony (details in materials and methods section A.7). If we apply the same logic for the effects of ayahuasca relative to placebo (fig. 2), we estimate the benefits of ayahuasca to be $2,703, or 484 times the $5.59 cost of the average ayahuasca dose.

4 Discussion and Conclusion

The legalization of psychedelics for treatment of depression and other conditions is being considered in many countries. But isolating the pure effect of the psychoactive drugs alone is complicated when bundled with psychotherapy. To that end, and following on from the FDA's rejection of MDMA-assisted treatment for PTSD, many companies are proceeding with clinical trials that would reduce or remove the therapeutic component *(14)*. The setting we study drops it entirely, in accord with traditional ceremonial practices.

Remarkably, we find that the center's one-time ayahuasca treatment durably reduces psychological distress and increases happiness relative to placebo (Cohen's $d \approx 0.4$). These effects are almost entirely driven by individuals who are distressed at baseline (Cohen's $d \approx 0.9$). Our findings suggest that the transformative effects of psychedelics documented in clinical settings may generalize to ritualistic use in legalized settings, even in the absence of therapeutic oversight. Furthermore, the group setting without therapy carries a ceremony price of only 24 USD, roughly the average daily wage in Brazil *(27)*. We conservatively estimate the well-being benefits to be roughly 200 times larger. By comparison, existing psychedelic-assisted therapy regimes are estimated to cost thousands of dollars per patient *(18, 33)*.

To our knowledge, this is the first randomized trial of psychedelic macrodoses that has the statistical power to compare efficacy across distressed and non-distressed subjects. Our finding that almost all of the benefit arises among the already distressed, and that there is an overall null effect on flourishing even among the distressed, suggests that DMT may be more effective at getting participants out of a rut, than elevating happy participants to more fulfilling lives.

Though many of the concerns regarding ingestion of such powerful psychoactive compounds outside the clinic can not be addressed in our setting, two can be. First, we do not see a greater prevalence of deteriorating well-being following bad or challenging trips relative to the placebo. Though recipients do report high rates of unpleasantness during the ceremony (diarrhea, vomiting, and dizziness), there are no adverse health effects beyond those experienced at ingestion. This speaks against the concern that while psychedelics improve well-being on average, they may worsen mental health for some *(34–36)*. Second, with respect to the concern of addiction: over the six month follow-up period, there are low rates of re-use, no evidence of increased use caused by treatment, and weak evidence, at best, of effects on ingestion of drugs other than ayahuasca.

The many other settings where psychedelics are legally available have rarely been utilized for randomized trials and are understudied. They have the potential to generate large samples in real-world settings, complementing the clinical findings that have been the main focus of research until now.

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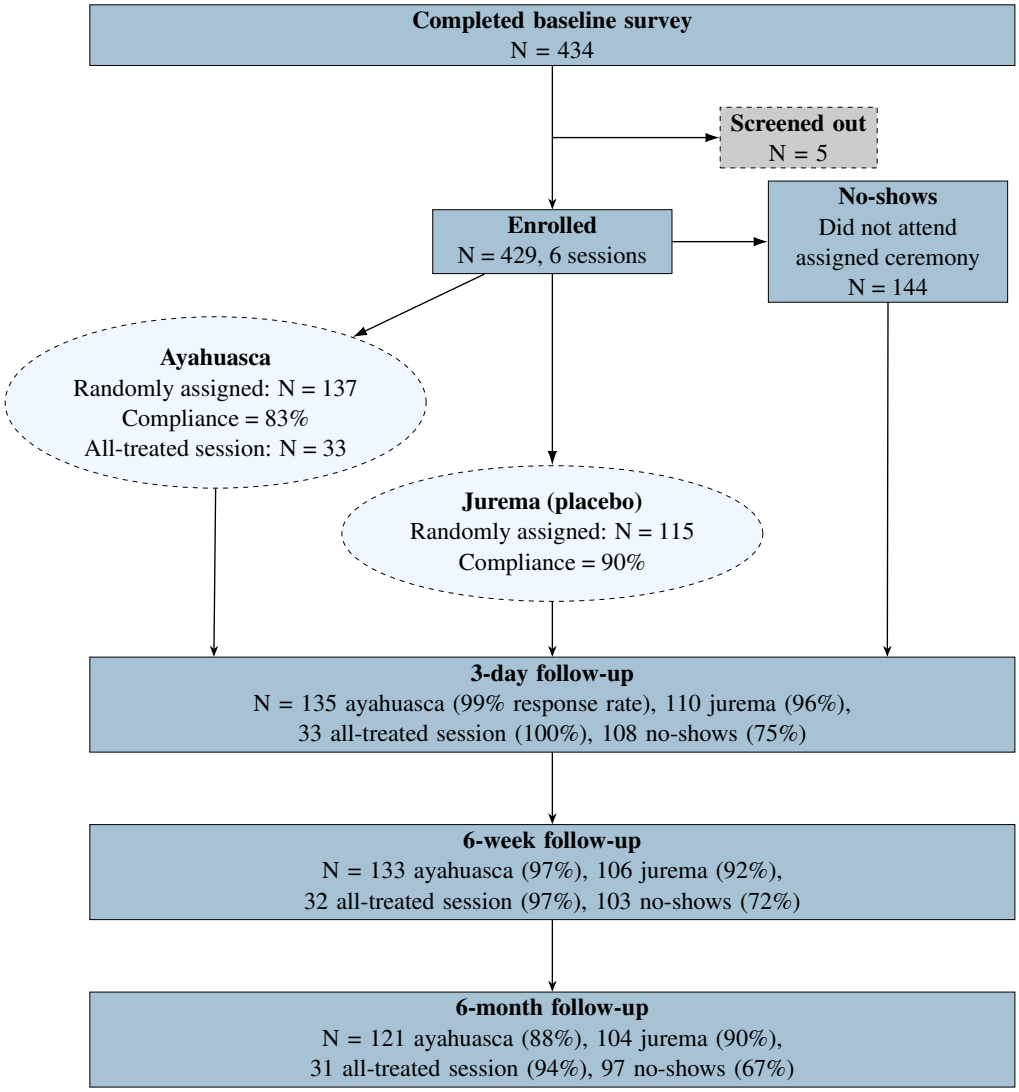
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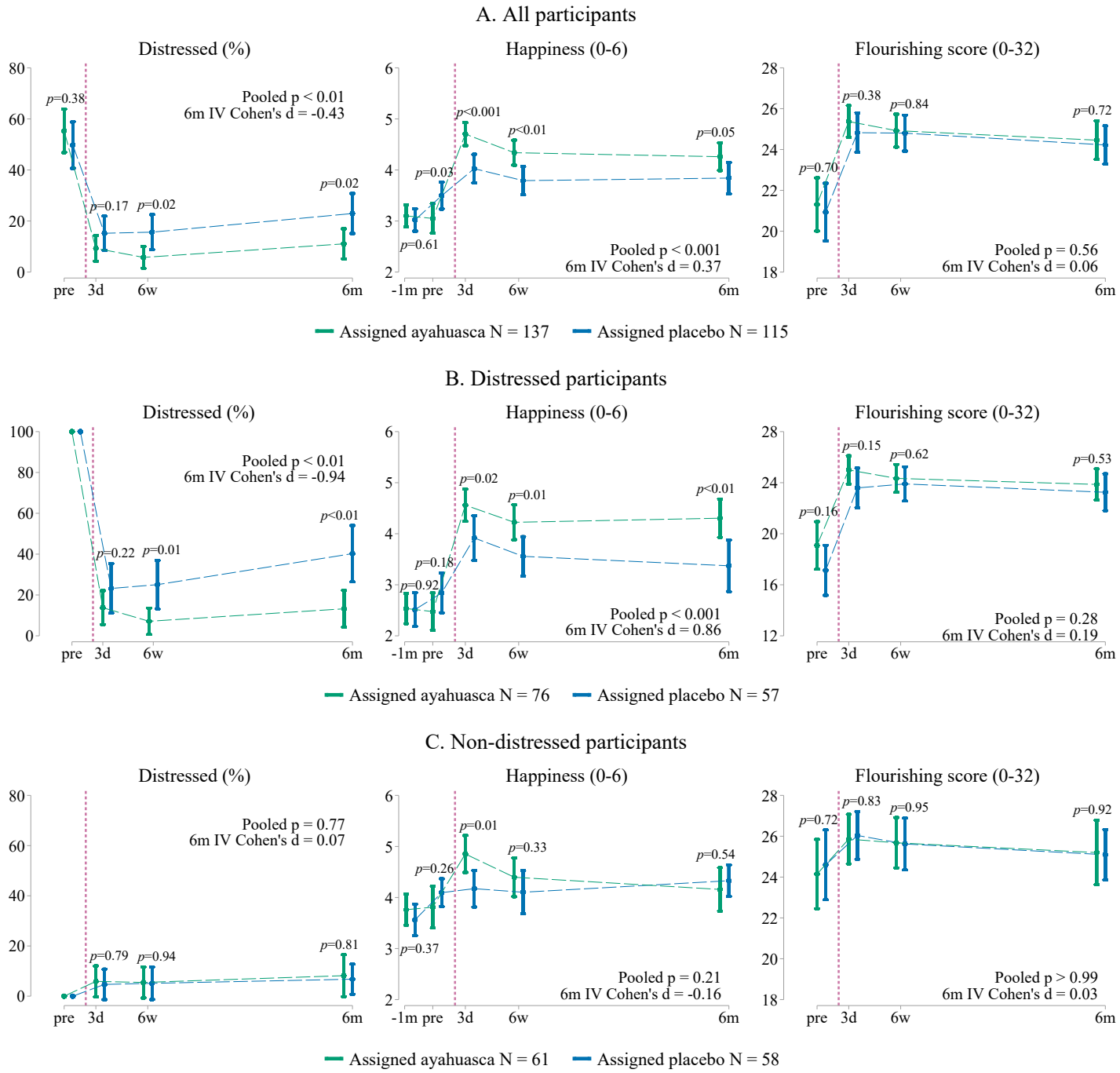
Figures and Tables

Fig. 1: Enrollment, randomization, and follow-up details



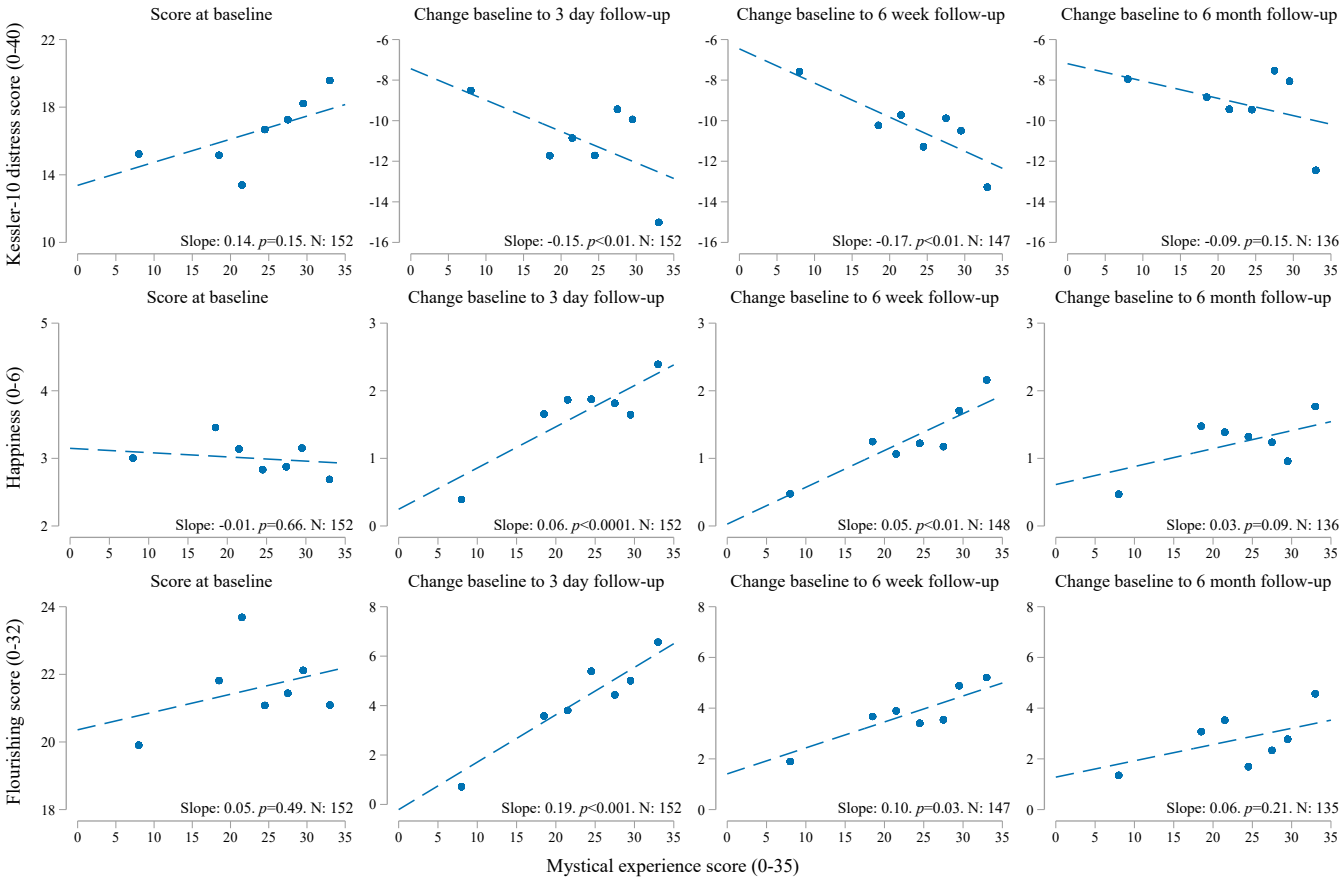
Note: The center screened out five participants with higher risks of psychosis identified through their personal and family medical history reported in the baseline survey. The center performed the randomization into ayahuasca or jurema before each session. *Compliance* refers to the percentage of participants who were actually given their randomly assigned treatment. In the last of the six sessions (All-treated session), by mistake, all 33 participants were given ayahuasca. Response rates to each follow-up survey are reported separately for four groups: those randomly assigned ayahuasca or jurema for the first five sessions, those in the all-treated session, and participants that did not attend their assigned session.

Fig. 2: Ayahuasca durably improves well-being relative to placebo



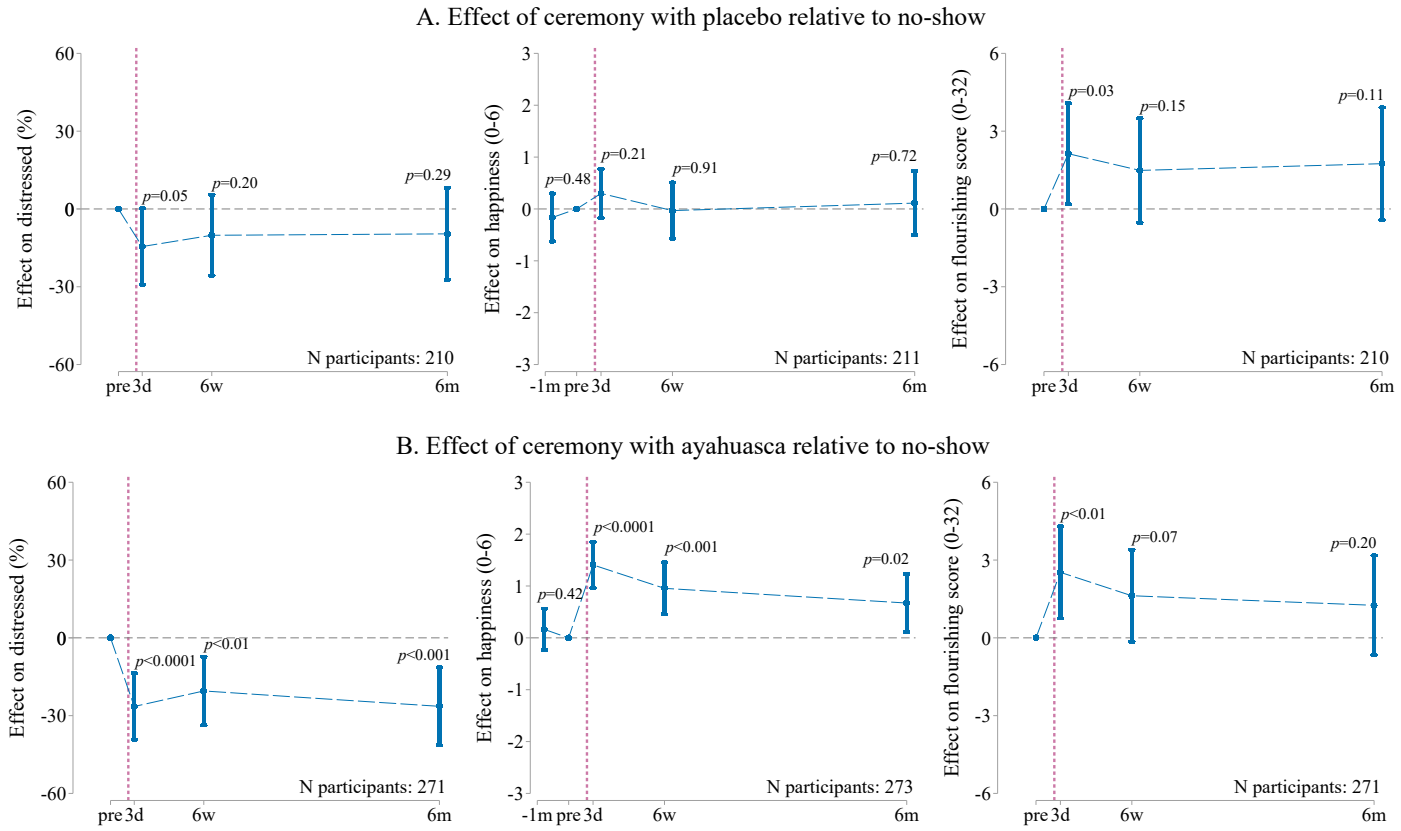
Note: Figure shows intent to treat effects. Baseline measures are denoted by pre, -1m denotes a retrospective measure for the past month. Distressed (%) is the percentage of participants that score 15 or above on the Kessler-10 Psychological Distress Scale. Happiness is the answer to *In general, how happy would you say you are these days?* on a scale from *Not very happy (0)* to *Very happy (6)*. Flourishing is the score from 0 to 32 from summing answers to eight statements like *I lead a purposeful and meaningful life (0 = Strongly disagree to 4 = Strongly agree)*. 95% confidence intervals are shown. *p*-values are from a regression that controls for the outcome at baseline (except for the baseline and retrospective comparisons) and session-by-gender fixed effects, with robust standard errors. The pooled *p*-value is obtained from a regression pooling data from the three follow-up surveys. 6m IV Cohen's *d* is the standardized effect of ayahuasca at six months, when using treatment assigned as an instrumental variable for treatment received. (**A**) presents results for the full sample of participants who attended one of the first five sessions (i.e. excluding those that attended the all-treated session), (**B**) restricts to distressed participants at baseline, while (**C**) restricts to non-distressed participants.

Fig. 3: More mystical trips predict greater improvements in well-being



Note: Each panel shows a binscatter plot correlating the mystical experience score (measured at the three-day follow-up) of participants that took ayahuasca with baseline measures of well-being (first column), and changes in well-being from baseline to each of the follow-up surveys (second to fourth columns). We use the raw Kessler-10 score rather than the indicator for a score of 15 or above to avoid floor effects (very few ayahuasca-takers are above this cutoff at the three-day follow-up). Each panel controls for session-by-gender fixed effects, and with the exception of the first column, the well-being outcome measured at baseline. Standard errors are robust.

Fig. 4: Ceremonies durably improve well-being when combined with ayahuasca



Note: Figure shows difference-in-differences effects of (**A**) attending the ceremony and taking the placebo relative to no-shows, and (**B**) attending the ceremony and taking ayahuasca relative to no-shows. As an example, the first coefficient in the top-left panel shows that the fall in percentage distressed from baseline to the three-day follow-up was almost 15 percentage points larger among those that attended and took the placebo than among those that did not attend the ceremony. 95% confidence intervals are shown, with standard errors clustered at participant-level.

Supplementary Materials

"Ayahuasca Without Therapy Durably Improves Well-Being"

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A Materials and Methods

A.1 Background and context

Ayahuasca. Ayahuasca is a traditional Amazonian tea that contains the hallucinogen N,N-Dimethyltryptamine (DMT) and monoamine oxidase (MAO-A) inhibitors. Similar to psilocybin, the active ingredient in magic mushrooms, DMT is a hallucinogenic tryptamine that acts as a serotonin receptor agonist *(37)*.

The use of ayahuasca for religious and ritualistic purposes is legal in Brazil, following a set of rules established in 2010 *(38)*. Our partner center has the necessary legal authorization that allows them to administer ayahuasca. Small-N studies have begun to document the potential anti-depressant effects of ayahuasca *(39–42)*, for a review see *(37)*, in parallel with a larger clinical literature on the anti-depressant effects of psilocybin *(1–4)*.

Ayahuasca has some immediate side effects, most commonly nausea and vomiting *(43)*. However, it is considered relatively safe in healthy individuals *(44)*. Animal studies indicate that the median lethal dose of DMT in humans would amount to 20 times more than that used in ceremonial ayahuasca practice *(45)*, and neither acute ayahuasca administration nor long-term consumption seems to be toxic to humans *(44)*. Use of the brew in religious ceremonies has a safety margin comparable to codeine, mescaline, or methadone *(45)*, with minimal risk of sustained psychological disturbance. Cardiovascular risk has been found to be low *(46)*, as has the addiction potential of the brew *(47)*. In fact, no serious conditions have been established when consumed by healthy individuals *(44, 48)*. Moreover, ayahuasca's safety has been shown on a variety of domains *(43)*, and the incidence of serious mental health consequences are extremely low *(34)*. Ex-post, our findings of no enduring adverse side effects and no subsequent addiction are consistent.

Jurema. We use jurema for our placebo condition. Jurema (*mimosa tenuiflora*) is a medicinal plant containing DMT that is already offered by our partner center. Like ayahuasca, jurema is served as a tea and is commonly used by indigenous people. Jurema has shown no toxicity in cancer and normal cells, and has antioxidant and antimicrobial actions *(49)*.

The ayahuasca brew is made of jurema plus a different plant that contains β-carbolines. When DMT is ingested orally it is broken down by the stomach enzyme MAO, and thus, has no psychoactive properties. β-carbolines are reversible MAO inhibitors that prevent DMT from being broken down, allowing it to have its psychoactive properties *(50)*. As a result, the key difference between ayahuasca and jurema is that, while they both contain DMT, jurema has no psychoactive effects and ayahuasca does. Our partner suggested jurema be used as a placebo,

given these features, along with the fact that they already offer jurema, and the fact that jurema looks similar in appearance to ayahuasca. For further information, and a review of the traditional use of jurema among indigenous peoples, see *(51)*.

Partner Center and Ceremony. Our partner center is in a large Brazilian city, and hosts roughly 1,400 ayahuasca participants per year. Unlike other ayahuasca centers in Brazil, our partner center holds universalist ceremonies—i.e. the center is not affiliated with any of the religions most associated with the use of ayahuasca as a sacrament (e.g. Santo Daime, União do Vegetal).

Each experimental session is attended by the two center owners and two center employees. The owners have over 13 years of experience with ayahuasca. The employees guiding the ceremonies ("guardians") have received over 80 hours of theoretical and practical training with ayahuasca, given by the center owners. During the ceremony, the owners and the guardians serve the ayahuasca and provide support when needed (e.g. by helping participants go to the toilet). The sessions are guided by music, with each study session using the same playlist.

A.2 Additional experiment design details

Recruitment, screening, and follow-up. Our partner recruited participants primarily through their social media and WhatsApp list, which is the status quo. The center continued to hold regular (i.e. non-research-related) ayahuasca sessions, which involved both current and first-timer users that they recruit. To first-time users, the center mentioned that they were recruiting first-time ayahuasca takers to attend a free session, with no mention of the research. Upon contacting the center to schedule their ayahuasca ceremony, the center asked whether they would like to participate in a study consisting of (i) random assignment to either a regular ayahuasca dose or a placebo jurema dose, (ii) responding to a survey before they take the ayahuasca, and (iii) up to three surveys afterwards. The center sent the baseline survey to those interested. We as the researchers sent the three follow-up surveys (hyperlinks to Qualtrics surveys) to participants.

Our partner center have status quo protocols regarding screening of people for ayahuasca. These protocols apply also for our experimental participants. We replicate them here, as described by the center owners:

1. The scientific literature says there is evidence of drug interaction with only one medicine, the antidepressant fluoxetine. But the center cannot suspend the use of this medication since it was prescribed by a doctor. So if a person takes it, the center doesn't ban them from going to the ceremony, it just gives a lower dose of ayahuasca.

2. There are concerns around taking ayahuasca if a participant has a background of schizophrenia. Participants who self-declare having a history of schizophrenia are excluded from participating.

These inclusion criteria are less stringent than typical inclusion criteria in clinical trials. But since these criteria are applied in the status quo (i.e. in the absence of our experiment), we keep them in tact for the experiment too. Otherwise, the center sends a set of instructions to sign-ups prior to the ceremony—telling them to check in with their doctor if they take certain medications, along with some guidance on what to bring and what to expect (see section B.1).

Participants in the study have their session cost waived, and receive 70 BRL (13 USD) for completing each of the first two follow-up surveys, and 100 BRL (18 USD) for completing the third follow-up survey—we increased the incentive for the third follow-up survey given higher expected attrition six months following the ceremony date.

Random assignment. The center used a random number generator to randomize the 429 participants 50:50 to ayahuasca or placebo, stratifying on session-by-gender. Since the study is single-blind, participants were not informed of their treatment status until the end of the six-week follow-up survey.

Of the 429 participants, 144 did not attend their assigned ceremony, while 33 attended the sixth session, where all participants were given ayahuasca due to error (fig. 1). For the remaining five sessions, 252 participants attended, with 137 of these having been randomly assigned to ayahuasca and 115 to the placebo. These numbers depart somewhat from 50:50 due to ayahuasca-assigned participants having a higher attendance rate than placebo-assigned participants. This difference in attendance is due to chance, given that participants did not know their treatment status in advance. Supporting this, baseline characteristics of the two groups of attenders are similar, and consistent with randomization (table S2).

Pledge not to take ayahuasca. Since ayahuasca is legally available in Brazil, one concern was that participants assigned to placebo would nevertheless take ayahuasca elsewhere in subsequent weeks, making it impossible to characterize long-term effects of ayahuasca. To mitigate this concern, in the baseline survey we asked participants to pledge not to take ayahuasca after the ceremony date until they had completed the six-week follow-up. We then ask participants detailed questions about ayahuasca and other psychedelic usage in the six-week and six-month follow-ups, telling participants that they should feel free to be honest (i.e. we won't mind if they broke their pledge). In practice, relatively few participants take ayahuasca after their assigned

ceremony dates, and we do not see a difference between those assigned ayahuasca and those assigned the placebo (fig. S3).

Dealing with repeat participants. Twelve participants entered the study twice—either both times as a no-show (i.e. they were scheduled to a ceremony, did not show up, then later they were scheduled to a second ceremony, and did not show up again), or one time as a no-show and one time as a ceremony attender. These participants were sent the follow-up surveys twice—once relative to the timeline of their first scheduled ceremony, and again relative to the timeline of their second scheduled ceremony. In the analysis, we keep only one set of surveys for each of these participants—i.e. we make it so that they only enter the study once. For the participants that were twice a no-show, we keep only the surveys they answered associated with their first scheduled ceremony. For the participants that were once a no-show and once showed up, we keep only the surveys they answered associated with the ceremony in which they showed up—we keep the latter, rather than the former, to maximize our statistical power for our more central test of the effect of ayahuasca relative to placebo. Since only a handful of participants entered the study twice, our results are nearly identical if we instead include the full set of survey responses, with standard errors clustered at the participant-level.

Ethical considerations. Our study received ethical approval from UBC (H21-00789 and H24-01148). Different from typical clinical studies, our study is in a setting in which ayahuasca is legal for ritual purposes, and our participants are those that were recruited by the center using status quo recruitment procedures—i.e. they had planned to take ayahuasca anyway in the absence of the study. Participation in the study then entails a lower probability of taking ayahuasca relative to the status quo (given the possibility of being assigned the placebo). Relatedly, our approach as the research team has been to have a clear division of labor: the center recruits participants as normal, following status quo screening criteria, and administers ayahuasca and jurema as normal. This way we are able to evaluate the effects of ayahuasca as it is already delivered in a legal setting. As the researchers, our role is to track outcomes by administering the follow-up surveys, and by analyzing the subsequent data.

A.3 Full survey questions

Well-being measures. We ask the following questions in the baseline survey and all three follow-up surveys.

Kessler-10 Distress (52). "Over the last [two weeks for baseline, three days for three-day follow-up, two weeks for six-week follow-up, four weeks for six-month follow-up], about how often have you felt..." [tired out for no good reason / so depressed that nothing could cheer you up / depressed / worthless / nervous / so nervous that nothing could calm you down / hopeless / restless or fidgety / so restless you could not sit still / that everything was an effort] [0 = Never, 1 = A little of the time, 2 = Some of the time, 3 = Most of the time, 4 = All the time. Summed to give a score from 0 to 40. Score of 15+ indicates moderate or severe psychological distress *(53).*]

Happiness. "In general, how happy would you say you are these days? Please use the scale below to indicate." [0 = Not very happy to 6 = Very happy.] At baseline we also ask the retrospective question, "In the past month, how happy have you felt?", and the prospective question, "Please guess how happy you will be in 6 weeks", with the same answer options.

Flourishing Scale (22). "Below are eight statements with which you may agree or disagree. Please indicate your agreement with each item." [I lead a purposeful and meaningful life / My social relationships are supportive and rewarding / I am engaged and interested in my daily activities / I actively contribute to the happiness and well-being of others / I am competent and capable in the activities that are important to me / I am a good person and live a good life / I am optimistic about my future / People respect me] [0 = Strongly disagree, 1 = Disagree a little, 2 = Neither agree nor disagree, 3 = Agree a little, 4 = Strongly agree.]

Subjective experiences. We ask the following questions in the first follow-up (three-day) to measure the acute subjective experiences of the participants that attended the ceremony (with some receiving ayahuasca, others receiving the placebo).

Meaningfulness. "How personally meaningful was the experience?" [0 = No more than routine, everyday experiences, 1 = Similar to meaningful experiences that occur on average once or more a week, 2 = Similar to meaningful experiences that occur on average once a month, 3 = Similar to meaningful experiences that occur on average once a year, 4 = Similar to meaningful experiences that occur on average once every 5 years, 5 = Among the 10 most meaningful experiences of my life, 6 = Among the 5 most meaningful experiences of my life, 7 = The single most meaningful experience of my life.]

Mystical experience questionnaire (7-item, (24)). "Please rate the degree to which at any time during your Ayahuasca session, you experienced each of the following phenomena." [Loss of feelings of difference between yourself and objects or persons in your surroundings / Loss of your usual sense of time / Feeling that you could not do justice to your experience by describing it in words / Feeling that you experienced something profoundly sacred and holy / Sense of awe or awesomeness / Gain of insightful knowledge experienced at an intuitive level / Feelings of universal or infinite love] [0 = None, 1 = So slight I cannot decide, 2 = Slight, 3 = Moderate, 4 = Strong, 5 = Extreme. Summed to give a score from 0 to 35.]

Ego dissolution (5-item). "Please rate the extent to which you have experienced any of the following statements during your Ayahuasca session. Please, slide the bar to indicate your answer, where 0 is 'No more than usually' and 100 is 'Entirely or Completely."' [I experienced a dissolution of my "self" or ego / I felt a sense of union with others / I felt far less absorbed by my own issues and concerns / I felt more special or important than others (reverse-coded) / I felt especially sure-of-myself (reverse-coded). Summed to give a score from 0 to 500.]

Open-text description of experience. "Describe in detail your experience with the Ayahuasca in the box below. Please be specific about what you saw, heard, and felt." [We use the total word count as another measure of the intensity of the experience.]

Trip domains. "If you had to describe a broad domain that you tripped on, what would that be? Select all that apply." [Family members / Revived old memories / Had visions / Love or peace / Sadness or pain / Confused and disordered thoughts / Relationships with people other than family members / Insights about bad habits / Insights about how to be happier / Happiness or pleasure / Relationship with nature / Other (Specify)] [We use the number of categories selected, and whether "Had visions" was selected, as additional measures of the intensity of the experience.]

Adverse effects. "We know that some people can have negative effects during an ayahuasca session. Did any of the following happen during your trip? Please select all that apply." [Vomit / Diarrhea / Dizziness / Bad trip / Challenging trip / Hypersalivation / Other (Specify) / None of the above]

Broader health and side effects. As secondary outcomes, we ask in all three follow-up surveys "All in all, how would you describe your state of health these days?" [0 = Very Poor / 1 = Poor / 2 = Fair / 3 = Good / 4 = Very Good], and in the six-month follow-up survey we ask "Do you experience any of the following? Check all that apply." [Increased heart rate / Increased blood pressure / Chest pain or tightness / Agitation / Dizziness / Confusion / Headaches / Visual disturbances / Paranoid thoughts and behaviors / Mood disturbances / Other negative health issue (Specify) / None]

Social desirability bias. To measure a tendency to give socially desirable answers, we ask participants a subset of the Marlowe-Crowne social desirability scale *(54)* in the baseline survey. In particular, we ask each participant to answer whether each of the following four statements is true or false for them: No matter who I'm talking to, I'm always a good listener / There have been occasions when I took advantage of someone / I sometimes try to get even, rather than forgive and forget / I am always willing to admit when I make a mistake.

Demographic measures. We ask the following questions in the baseline survey.

Race. "What is your race?" [White / Black / Yellow / Indigenous] (note that these are standard categories for race when asked in surveys in Brazil). We code participants as *Not White* if they do not select "White."

Education. "What is your highest level of education?" [0 = Less Than Middle School / 1 = Middle School (Incomplete) / 2 = Middle School (Complete) / 3 = High School (Incomplete) / 4 = High School (Complete) / 5 = Technical Degree / 6 = University (Incomplete) / 7 = University (Complete) / 8 = Other Post Graduate / 9 = Masters / 10 = PhD].

Income. "In the last 12 months, what was your average gross monthly income? Please, consider the average of all your income, including salary, rent, fees, and others." [0 = 0 to BRL500 / 1 = BRL501 to BRL1,000 / 2 =BRL1,001 to BRL2,000 / 3 = BRL2,001 to BRL3,000 / 4 = BRL3,001 to BRL5,000 / 5 = BRL5,001 to BRL10,000 / 6 = BRL10,001 to BRL20,000) / 7 = BRL20,001 to BRL100,000 / 8 = BRL100,001+].

Employment. "What is your current employment status?" [I am employed in the formal sector (that is, with a contract) / I am employed in the informal sector / I am an independent worker / I am unemployed / I'm retired]. We then code participants as *Employed* if they select one of the

the first three options, and as *Employed in Formal Sector* if they select the first option.

Work Satisfaction. "How satisfied are you with your current job?" [0 = Very unsatisfied / 1 = Unsatisfied / 2 = Indifferent / 3 = Satisfied / 4 = Very satisfied]. This question is asked to those that report being employed.

Family History. "Are any of the symptoms below present in your family? Select all the applicable options." [Schizophrenia / Depression / Alcoholism / None]. For each option, we create a variable equal to 1 (and 0 otherwise) if the participants selects the option.

Cares What Others Think. "Please indicate below how much do you agree with the following sentence: I care a lot about what other people think of me." [0 = Strongly disagree / 1 = Disagree / 2 = Neither agree nor disagree / 3 = Agree a little / 4 = Strongly agree].

Depression Last Month. "In the past month, how depressed did you feel?" [answer from 0 = Not very depressed to 7 = Very depressed]. Unlike our analysis of effects on happiness, we do not use this variable as a retrospective measure of distress as this question is not comparable with our other measures of distress (which use the Kessler-10 Scale).

A.4 Estimation

Intent to treat. For our intent-to-treat analysis (fig. 2), we estimate the following regression, keeping only the participants that attended their assigned ceremony:

$$y_{it} = \gamma_s + \beta_{0t} y_{i0} + \beta_{1t} \text{Assigned Ayahuasca}_i + \varepsilon_{it} \tag{1}$$

We run this specification for the five experimental sessions in which there was variation in actual treatment (i.e. we drop the sixth, in which due to an error all attendees were given ayahuasca). We run it separately for each outcome y (distressed, happiness, flourishing), and for each timepoint t (baseline, three-day, six-week, and six-month). For happiness, we have a fourth timepoint, since we also have a retrospective measure at baseline, where participants recall their happiness over the past month.

y_{it} is the well-being outcome for participant i in survey t, while γ_s are randomization strata (gender-by-session) fixed effects. With two genders and five sessions, these are ten dummy variables. For $t \in \{3\text{d},6\text{w},6\text{m}\}$ we control for the outcome measured at baseline (y_{i0}). While we do not need to control for this variable for unbiased estimates of causal effects (since we have

random assignment), we do so to increase the precision of our estimates.

The key regressor is Assigned Ayahuasca$_i$, which is equal to one if the participant was randomly assigned to receive ayahuasca, and equal to zero if the participant was randomly assigned to receive the placebo. It follows that $\hat{\beta}_{1t}$ is our intent-to-treat estimate of the effects by time t of being randomly assigned to receive ayahuasca. We estimate robust standard errors. The p-values for each timepoint in Figure 2 then come from a test of the null hypothesis that $\beta_{1t} = 0$.

To estimate the means and confidence intervals for the treatment and control groups separately, while accounting for the strata fixed effects and baseline control, we adapt equation 1. In particular, we regress the outcome on a dummy for being assigned to ayahuasca, a dummy for being assigned to jurema, de-meaned strata fixed effects, and the de-meaned baseline measure of the outcome. We then plot the coefficients and confidence intervals on the two treatment dummies. This approach ensures that the gap between treatment and control is equivalent to the $\hat{\beta}_{1t}$ that we estimate using equation 1.

To obtain the pooled p-value in fig. 2, we stack the observations from the three follow-up surveys, allowing a given participant to have up to three rows in the dataset (depending on how many follow-up surveys they completed). We then estimate equation 1 above, but with the strata fixed effects and baseline control fully interacted with dummies for each of the follow-up surveys, and with standard errors clustered at participant-level. The pooled p-value is then from the same test of the null hypothesis that $\beta_1 = 0$.

For the 6-month IV Cohen's d, we also run a variant of equation 1 above. The only differences are: (i) we standardize the well-being outcome by demeaning and dividing by the pooled standard deviation, (ii) we estimate effects for $t = 6$ months, and (iii) we use assigned treatment as an instrumental variable for actual treatment, and report the second-stage effect of actually taking ayahuasca *(25)*.

Trip quality and well-being effects. For our exploration of how trip characteristics mediate effects (fig. 3), we estimate the following regression, keeping only participants that actually received ayahuasca, which this time includes participants in all six experimental sessions:

$$\Delta y_{it} = \psi_s + \phi_0 y_{i0} + \phi_1 \text{Mystical Experience Score}_i + u_{it} \tag{2}$$

where Δy_{it} is the change in the well-being measure from baseline to follow-up survey t, ψ_s are session-by-gender fixed effects, and y_{i0} is the well-being measure at baseline. The key regressor is Mystical Experience Score$_i$ (0 to 35), measured in the three-day follow-up, which captures the mystical nature of the trip experience. In the first column of Figure 3, the left-hand-side variable is instead the baseline measure, y_{i0}, and accordingly, these regressions do not include

the baseline measure as a control variable. We estimate robust standard errors.

In each panel of Figure 3 we report the slope (i.e. $\hat{\phi}_1$), and a p-value that tests the null hypothesis that the slope is equal to zero. We also show the binscatter based on the same specification (i.e. still controlling for strata fixed effects and the baseline-measured well-being outcome), with seven bins throughout.

Difference-in-differences. While we track outcomes for those that did not attend their assigned ceremony (no-shows), we cannot use simple mean comparisons to estimate effects of ceremony attendance, since the no-shows were not randomized. Reflecting this, we can see that no-shows differ somewhat from jurema-takers in terms of their baseline characteristics—they are less educated, less happy, and more distressed (column 9, table S2).

Instead, we use a difference-in-differences approach, in which we effectively test for whether the *improvement* in well-being from baseline to each follow-up is larger for those that attended the ceremony than for those that did not attend *(26)*. For these effects to be interpreted as causal, we rely on the assumption of parallel trends—i.e. that in the absence of attending the ceremony, well-being in the two groups (no-shows versus attenders) would have trended similarly. In our baseline, participants report their current happiness as well as their recalled happiness over the past month. This allows us to test for parallel *pre*-trends (though with the caveat that this test relies on the assumption of accurate recall), which we find evidence for (see central column, fig. 4), giving suggestive evidence in favor of the parallel trends assumption.

Our core difference-in-differences specification is:

$$y_{it} = \alpha_i + \alpha_{st} + \theta_1(\text{Attended}_i \times \text{3-day Follow-up}_t) + \theta_2(\text{Attended}_i \times \text{6-week Follow-up}_t) + \theta_3(\text{Attended}_i \times \text{6-month Follow-up}_t) + e_{it} \quad (3)$$

where there are now up to four observations per participant (for t = baseline, three-day, six-week, and six-months), and y_{it} is defined above. α_i are participant fixed effects, while α_{st} are randomization strata fully interacted with follow-up survey fixed effects. Attended_i is equal to one if participant i attended their assigned ceremony, and equal to zero otherwise (i.e. for no-shows). 3-day Follow-up_t is equal to one if $t = 3$ days, and similarly for 6-week and 6-month. We keep only the participants that completed the baseline and answered at least one follow-up survey. We cluster standard errors at the participant-level.

In fig. 4 we plot the point estimates and 95% confidence intervals for θ_1, θ_2, and θ_3.[3] These

[3] In the happiness panels, we run a specification that also includes an interaction between Attended_i and

are our difference-in-differences-estimated effects of attending the ceremony on well-being at each timepoint. The p-values that we plot test the null hypothesis that each of these coefficients is equal to zero.

To get at the effects of attending and taking the placebo, we run the regression keeping only those that didn't attend or attended and took the placebo. To get at the full effects of attending the ceremony and taking ayahuasca, we keep only those that didn't attend or attended and took ayahuasca.

A.5 Additional results (mostly robustness)

Ayahuasca versus placebo. In the main text we report that ayahuasca increases mystical experiences, ego dissolution, and meaningfulness relative to placebo. Ayahuasca also causes participants to have trips that touch on more areas of life, to have more visions (hallucinations), and to write 56% more in an open response question asking them to describe their experience (columns 4 to 6, table S6).

The effects of ayahuasca relative to placebo on psychological distress are similar if we use the raw Kessler-10 score, or the six-item version of the score *(55)*, rather than the indicator variable for having a K10 score of 15 or above (fig. S6).

The well-being effects of ayahuasca relative to placebo are similar, though more precise, if we instead compare groups based on actual treatment, as opposed to assigned treatment. In addition, the six-month standardized IV effects are smaller, at roughly 0.3 (fig. S7). Comparing groups based on actual assignment, rather than random assignment, may be reasonable, as the center's deviations from randomization appear to be arbitrary—participant characteristics are for the most part similarly balanced if we compare groups based on actual assignment (column 5 of tables S2-S5).

Given that our well-being measures are self-reported, one concern might be that our effects are inflated by experimenter demand effects—in which participants over-report their well-being when treated, and vice versa when in control, in order to help the experimenter. Such demand effects are typically small *(56)*. Nevertheless, we explore this concern by testing for whether the positive effects on well-being are driven by participants that give more socially desirable answers at baseline *(54, 57)*. We do not see evidence of this (table S10), suggesting that experimenter demand effects are unlikely to be biasing our findings.

In the main text, we report that the well-being effects of ayahuasca are driven by the partici-

Retrospective Report at Baseline$_t$, where the latter is a dummy variable equal to one for a participant's retrospective report of happiness over the past month, answered in the baseline survey. This is what permits a test of parallel pre-trends.

pants that are distressed at baseline. We see a similar pattern of results if we instead split by the median of baseline happiness (fig. S8).

Trip quality and well-being effects. We report in the main text that challenging trips deliver well-being gains relative to placebo, while well-being gains following bad trips are similar to those in the placebo group. We use reports from the three-day follow-up to characterize how bad and challenging trips differ from other trips (fig. S9).

Participants that report having had bad trips are more likely to have had negative side effects (diarrhea, dizziness, hypersalivation), and they are more likely to have faced sadness and pain, and confused and disordered thoughts as part of their trip experiences (left panel, fig. S9). Nevertheless, they report a higher likelihood of having had visions and insights about bad habits. The differences between challenging and non-challenging trips are somewhat similar (right panel, fig. S9), though most trip domains are more likely to be reported by those that had challenging trips. This matches with the view of the owners of our partner center: that a trip being challenging can actually be a good thing.

Ceremony effects. As described in the main text, our difference-in-differences approach to estimating the effects of ceremony attendance relies on a parallel trends assumption—no-shows and ceremony attenders should have had the same trends in well-being had the ceremony never happened. Since no-shows have lower well-being at baseline (table S2), one particular concern would be that those with lower well-being initially would trend differently than those with higher well-being. To allow for these differential trends by baseline well-being, we re-estimate our difference-in-differences regressions after adding interaction terms between baseline well-being and each of the follow-up survey indicators. When we do so, the effects of ceremony attendance are somewhat more positive (fig. S10), making our cost-benefit analysis in the main text conservative.

A.6 Placebo effects

Personal expectation may play a role in affecting psychedelic experiences, although evidence on expectancy effects is mixed *(58, 59)*. Related, subjective experiences have been argued to be necessary for psychedelics to have enduring well-being benefits *(32)*, suggesting that blinding may be neither possible, nor desirable, in assessing efficacy. But this then raises the question of how to deal with placebo effects *(60)*, leading some to argue that when unblinding is present, any evidence in support of efficacy is weak *(61)*.

To shed light on functional unblinding, at the first follow-up we asked participants to guess which treatment they had actually received. Unfortunately, we made an error in the question text, due to a holdover from a previous survey. Instead of being asked to guess whether they had received ayahuasca or the placebo jurema, we asked:

In your Ayahuasca session, you could take either a regular Ayahuasca dose or a less concentrated Ayahuasca dose. If you had to guess, which one would you say you took? We are going to tell which Ayahuasca dose you took by the end of the next survey, which we will send in 6 weeks. [Answer options: Ayahuasca with regular concentration / Ayahuasca with lower concentration (i.e. weaker)]

This formulation of the question likely confused participants, given that all previous communication (including in the consent and in the ceremony) explained that the two possible treatments were ayahuasca or jurema, a medicine with DMT but no psychedelic effects. Nevertheless, we take the participant's answer to this question to be a crude proxy for the participant's belief that they received ayahuasca—i.e. we presume that those that answered "regular concentration" are more likely to believe they received ayahuasca than those that answered "lower concentration."[4]

Using the answers, we see a clear signal of functional unblinding: 75% of those that received ayahuasca guess that they were given the regular concentration, compared with only 9% of those that received the placebo.

Accounting for placebo effects. We use two approaches to explore the possibility of placebo effects. Both approaches are imperfect, not least because they rely on the guess question with the misleading wording. As a result, we consider this analysis to be suggestive, and we do not describe these results in the main text.

First, we run specifications 1 and 2 defined above, adding an extra control variable: a dummy variable equal to one if the participant guessed that their actual treatment was regular concentration ayahuasca. The effects of ayahuasca relative to placebo, and the effects of more versus less mystical trips are similar after adding this control (figs. S11, S12), though the estimates are less precise in the former case. The results of this first approach speak against a large role for placebo effects.

The second approach takes advantage of the fact that we reveal each participant's actual

[4]Note also that, to the extent that the question wording confused participants, we may have inadvertently nudged participants towards thinking that they all received ayahuasca. This would have the benefit of weakening the role of placebo effects in driving differences between treatment groups.

treatment status at the end of the six-week follow-up survey (with the correct wording). For the sake of this exercise, we assume that participants that guessed they received the low-concentration ayahuasca actually believed that they received the placebo, jurema—i.e. we assume that they remembered what the true treatment options were.

For some participants, the revelation of the actual treatment received at the six-week point is a shock to their beliefs—some thought previously that they were treated, but now learn that they were not, and vice versa. For other participants there is no shock to their beliefs—their guess is revealed to have been correct. These two types of participants allow us to run a variant of a difference-in-differences specification—effectively comparing whether participants that learn that they were actually treated (control) have larger (smaller) improvements in well-being from the second to the third follow-up survey than those that were correct about their treatment all along. The specification is:

$$y_{it} = \alpha_i + \alpha_{st} + \gamma \text{Believe Took Ayahuasca}_{it} + e_{it} \tag{4}$$

where we keep only participants that attended their assigned ceremony, and only their answers to the 6-week and 6-month follow-up surveys. y_{it} is as defined above, while α_i are participant fixed effects, and α_{st} are randomization strata fully interacted with indicators for each follow-up survey. Believe Took Ayahuasca$_{it}$ is a dummy variable equal to one if participant i believes at the start of follow-up survey t that they were given ayahuasca during the ceremony they attended. For $t =$ 6-week this belief is based on the participant's guess during the 3-day follow-up survey (assuming that a participant that guesses low-concentration believes they received the placebo), while for $t =$ 6-month the belief is set to the truth, given that treatment status is revealed at the end of the 6-week follow-up survey.

As a test for parallel pre-trends, we run the same specification, but keeping only survey answers to the 3-day and 6-week follow-up surveys, and replacing the key regressor with Believe Took Ayahuasca$_{i,t+1}$. This tests for whether participants that would later learn that they were treated (control) were already trending towards improved (worsened) well-being than participants that would learn that they guessed correctly.

Using this approach, we see some suggestive evidence that participants who learn at the six-week follow-up that they received ayahuasca have greater improvements in well-being six months later than those who learned that they did not (columns 1 to 3, table S11, though only one of three effects is statistically significant, with $p = 0.08$), and these effects are not driven by pre-existing trends (columns 4 to 6). Accordingly, we do not rule out that placebo effects play a role in the observed effects on well-being.

A.7 Cost-benefit analysis

We discuss two cost-benefit analyses in the main text: the first comparing the depression-reduction benefits of attending a ceremony and taking ayahuasca (relative to not attending) with the per-person price of the ceremony set by our partner center (24 USD). The second compares the depression-reduction benefits of receiving ayahuasca (relative to the placebo) with the per-person procurement cost of the ayahuasca itself.

Ceremony versus no-show. To estimate the benefits, we use the three difference-in-differences coefficients in the far-left panel of fig. 4B, and calculate the area between the grey dashed line at zero and the blue dashed line. This area gives the number of distressed years averted due to the ceremony under the assumptions that (i) the difference-in-differences estimates are unbiased estimates of causal effects, (ii) after six months there is no treatment effect of the ceremony (a conservative assumption), and (iii) treatment effects grow or fall linearly in between each of the four timepoints (baseline, three-day, six-week, six-month).

Using equation 3 above, we estimate the number of distressed years averted X to be:

$$X = ((3/365) \times \hat{\theta}_1 \times 0.5) + ((42-3)/365) \times (\hat{\theta}_1 + \hat{\theta}_2) \times 0.5) + ((182.5 - 42/365) \times (\hat{\theta}_2 + \hat{\theta}_3) \times 0.5)$$

which is the sum of the area of one triangle (capturing the effects in the first three days) and two trapezoids.

In the next step, we have to value the number of distressed years averted in dollars. We first convert a single distressed year averted to its DALY (disability-adjusted life year) equivalent, by applying the disability weight of 0.396 used by the Global Burden of Disease 2021 for moderate major depressive disorder.[5] Here we are taking moderate or severe distress according to the Kessler-10 scale (a score of 15 or above) to be approximately equivalent to a moderate major depressive disorder (the Global Burden of Disease does not have a disability weight for psychological distress itself). Finally, we value a DALY at 100,000 USD, following Open Philanthropy.[6] The benefits then amount to $0.396 \times 100,000 \times X$ USD, where X is the number of distressed years averted, defined above. We verified that our approach to valuation closely follows that of Open Philanthropy through personal correspondence with an Open Philanthropy research fellow on the Global Health and Well-Being cause prioritization team.

[5] See https://ghdx.healthdata.org/record/ihme-data/gbd-2021-disability-weights.

[6] See https://www.openphilanthropy.org/research/technical-updates-to-our-global-health-and-wellbeing-

Ayahuasca versus placebo. Our approach to valuing the depression-reduction benefits of ayahuasca relative to placebo follows similar steps. The key difference is that we use instrumental variables estimates of the causal effects of ayahuasca to estimate the number of years of depression averted, as opposed to difference-in-differences estimates (i.e. we use the IV version of equation 1, in which we use Assigned Ayahuasca as an instrumental variable for Took Ayahuasca). These estimates of the benefits are then more credible, given that they do not rely on a parallel trends assumption.

Otherwise, to calculate the cost of the average participant's ayahuasca, we use the fact that the ayahuasca costs the center 400 BRL/liter, and the average dose in our experimental sample is 78.2 ml. The cost per person is then 31.3 BRL, or 5.59 USD.

B Supplementary Text

B.1 Ceremony Instructions

Prior to the ceremony, the center provides the following instructions (in Portuguese) to those that signed up (whether for one of our experimental sessions, or for one of the regular sessions outside of the experiment):

RECOMMENDATIONS FOR THE RITUAL WITH AYAHUASCA

For the Ritual:

- *Take a blanket or blanket and cushion to stay comfortable during the session, these items are very important for your comfort and well-being.*
- *Bring a 500 ml bottle of water to keep by your side.*
- *We serve a delicious soup at the end of work.*
- *Bring a plate of sweet or savory (vegetarian), juice or even fruit to share at the end of the ritual.*
- *The participant is not allowed to wear shorts, short skirts or low-cut clothing, remember that you are coming for a rite and we ask your clothes to be discreet and comfortable.*
- *Avoid black clothes, try to wear light colored clothes.*
- *Carrying any type of weapon is prohibited.*
- *It is not permitted to record, film or photograph during the session.*
- *Avoid sexual intercourse two days before the Ritual.*
- *Try to be with yourself and focus on what you are looking for from the experience.*
- *Do not drink alcoholic beverages or use drugs (including psychiatric drugs) two days before the session. During the session, the use of any type of drug is prohibited. We ask that if you use cannabis (marijuana), you do not use it 2 days beforehand.*
- *In the two days before the ritual, please take care of your diet, by not eating red meat, avoiding sexual intercourse, as well as preserving your body and spirit from fights and confusion.*

- *Try to eat up to a maximum of 2 hours before the start. The last meal should be light, preferably without any type of meat, fatty foods, fried foods, spicy, highly seasoned and sweet foods. Give preference to cereals, vegetables and fruits.*

During the ritual:

- *Try to stay connected to your breathing (soft, deep, calm), without unnecessary tension, with your eyes closed and your mind focused on the heart – home of the Natural Being – trying to stick to the guidance, music and calls.*
- *Leave cell phones and any electronic sound devices turned off.*
- *Smokers are not discriminated against, but they are asked not to smoke during the ceremony.*
- *It is not allowed to talk or touch other participants, except the facilitators. It is also important to try to remain seated and calm, avoiding sudden movements that could disrupt the concentration of others.*
- *If you need help and/or notice that someone needs help, call the designated facilitators and Guardians, avoiding any type of personal intervention with other participants, unless requested by a facilitator.*
- *After the Ritual, you may feel sensitive and therefore it is recommended to avoid tense emotional states, arguments, etc. Try, again, to be in peaceful and pleasant environments, if possible, take the next day off and look for a place with plenty of greenery to rest or meditate. The day after the session, avoid alcohol and drugs.*

Restrictions for drinking Ayahuasca:

- *Minors can only participate with written authorization with a notarized signature from their parents or guardians. [Note: this instruction regarding minors applied only to the non-experimental sessions]*
- *People who use antidepressants such as selective serotonin reuptake inhibitors or monoamine oxidation inhibitors (MAOIs) such as fluoxetine, citalopram, paroxetine, sertraline or tranylcypromine should consult their doctors, seeking appropriate authorization, avoiding risks to their health. In this case, they may consider stopping the medication for two days or changing the antidepressant, etc. by a medication from another category.*

- *People with a history of a psychotic break, previous psychiatric hospitalization or who are taking other medications, such as anorexics (weight loss medication) should first contact us for clarification.*
- *People who have consumed alcoholic beverages or heavy drugs two days before the session are prohibited from participating in the session.*

Gratitude!

B.2 Ceremony Lecture

Below are excerpts from an English translation of the lecture given for an experimental session in October 2023, on the topic of happiness.

"I ask everyone to go to their mat, because we are going to start the work now, I will also give you some instructions on what this experience will be like... Ayahuasca is a medicine considered one of the oldest in the world, there are records from 100 years ago, 1930. This tea was brought by Raimundo Irineu Serra, from the Atlantic Forest to modern civilization, our Brazilian society knows this medicine from 1930 and Ayahuasca began to be increasingly used. The last census carried out in February 2022, showed that around 576 thousand people practiced this medicine, it is a relatively large number but when we look at a population of around 210 million inhabitants, it represents a little 0.25% of the population. The experience you will have tonight is still a taboo for Brazilian society. It is an experience used for millennia, with the purpose of healing people. Healing can be understood in different ways, Ayahuasca brings us more clarity about our lives, situations, and ourselves. Ayahuasca is used to get to know ourselves. A large part of the population, if you ask, says they know each other, but in reality, we know very little about each other. It's as if we were a machine with enormous potential and we don't know how to use it, as if we were a Ferrari, but we don't know how to drive it. What's the point of having a Ferrari if we don't know how to exploit its potential? We are a Ferrari and we can know how to use it, if we understand our instruction manual, and understand how we work.

Have you ever heard of the term consciousness expansion? It is a mechanism in which Ayahuasca can bring this to you. Defining expansion of consciousness is not easy, many of us hear about it but don't know exactly what it is. I would like to invite you to a very didactic definition. Imagine that each of you is this room that we are in here and all these objects are characteristics of you, things that are part of you. Now imagine that I turn off the lights, cover all the windows, seal all the cracks in the doors, so that there is total darkness inside this room.

Are you still you? It's still you with all your characteristics but you can't see anything because it's dark and you end up bumping into things and you can't find the tools that can help you. Now imagine that I go to the window and make a hole in the window and that through this beam of light you can see a small part of the room. This little light inside the room is called consciousness, it's what [CENTER OWNER'S NAME REDACTED] knows about [CENTER OWNER'S NAME REDACTED] and it's what you know about him and that's why 99% of people when they say they know who they are, they are correct, because they don't they know the whole room, but only that small area. Some people don't understand what happens in their life because they only know what happens in that small area. The expansion of consciousness allows me to go to that window, open it and that beam of light will allow me, for the first time in my life, to illuminate an area of the room that I had never seen before.

Will drinking this tea clear my vision? No! I've been drinking this tea for 15 years and every time it lightens a little more, it lightens little by little, we can access areas, characteristics, and situations that I had never seen before. I always tripped over this chair every day, now I see this chair. A few hours after taking Ayahuasca, the beam of light returns to the size it had before and it's not that it doesn't do anything, because the Ayahuasca process is 100% conscious, everything done today you will remember tomorrow. You may not be seeing the chair but you will remember that you saw the chair. Ayahuasca is not a miracle tool because in the 15 years I have been using it, it has never removed the chair for me, I am the one who has to remove the chair, it just shows me. It clearly shows situations in your life that can be modified so that you can perform better in life. What do I call performance? It depends on each person, what you are looking for in life. The fact is that many people in life believe that performing well in life means having a more satisfying life, being able to fulfill more of their desires, earning more money, this concept changes after this experience, as we begin to have access to things that are outside the clear area, what is inside the clear area were things that we were often taught from an early age, a certain path to personal fulfillment: the path to success, the path to making money in what you do, which are valid and which are really good for us, but the room is not just that and that night you will be able to gain access.

In this culture, we learn a mold that human beings must fit into, mold themselves into to be socially accepted. The problem is that a lot of the time, being socially accepted in this way is not making you complete, happy. You wake up, spend energy, try hard, do your best, but you feel like you're not complete. There's something missing for all of us, I'm nothing different from you because I've been drinking tea for 15 years, but I have many different things from [CENTER OWNER'S NAME REDACTED] 15 years ago. Ayahuasca brings much more clarity to issues in my life, things that I waste less time on, for example things that are bad for

me. Today, I banish it from my life or I don't allow it to harm me, as I did in the past, like negative emotions, negative thoughts.

One of the most wrong things, in my opinion, that they teach children, to everyone, every day, is that pleasure and happiness are very similar things. Pleasure and happiness are extremely different things. If we stop to think about this moment, there are some people in this city who are feeling a lot of pleasure right now, they are living in a wonderful neighborhood in [PLACE REDACTED] called Cracolândia. I assure you that they are feeling a lot of pleasure, but are they happy? Certainly not. Part of us learns that we will only be happy if we manage to do everything we want: 'I'll be happy the day I no longer have problems, the day my life is all right, the day I no longer have a headache with nothing,' forget it, this is a childish fantasy, this won't happen, a problem is something that people will always have. And amazingly, problems are good for our growth. Happy people are not people who don't have problems, they are people who learn to manage their problems. Do you realize that it has nothing to do with doing everything I want to do? The unhappiest people I know are the people who do whatever they want to do. Often, happiness lies more in the renunciation of desires than in their fulfillment. I'm not referring to all desires, I'm not saying that pleasure is bad. I am inviting you to analyze your life to understand that many of your sufferings, the problems you have today are associated with the search for this pleasure.

...There's a phrase like this: Don't poke the jaguar with a short stick. I say: don't poke the jaguar with a long stick or any stick, stay away from the jaguar. When we identify something in our lives that is dangerous to our happiness, to our growth, the best thing you can do is stay away from that danger. A strong human being is not one who has no weaknesses, but one who knows the weaknesses he has. When you know yourself, you know your weaknesses, you can prevent yourself from falling into a hole. I stayed away from the jaguar, because the jaguar and I already had something that only hurt me, that only hurt me and I don't want to fall into that again. Each person must identify their temptation. The problems I had were different from what I have today when I arrived in this house 15 years ago, I continue to have problems and challenges not to fall into the hole. Some things we learn from pain, other things you don't need to suffer to learn. Ayahuasca taught me many things about love, when I arrived I had hit my head a lot. Ayahuasca was my last resort, I tried many things to improve my living conditions. I didn't suspect that she would change my life as much as she did. The reference we have for this medicine is not because it is our work, everyone who works with this medicine has had a very beautiful life transformation. She saved our lives and I'm sure she can do that in your life too...

...It has two important active ingredients: the main active ingredient that expands conscious-

ness, which is called dimethyltryptamine or DMT, which is a chemical molecule very similar to a substance we have inside us called serotonin. Serotonin is a neurotransmitter that exists within me, within you, within every living being, which is important for a series of metabolic processes to occur, mainly for the functioning of our central sector, thought, cognition, all of this depends on serotonin. Our brain activity works through serotonin, there are also other substances, but it is the main one. This dimethyltryptamine or DMT is so similar to serotonin that it activates the same serotonin receptors throughout your body and with this, we get the effects of serotonin but with one difference, the quantity. It's as if you've taken a flood of serotonin into your body. But serotonin is modeled in our body, we produce it and it remains at a very high rate, then another substance comes to reduce this rate, Monoamine oxidase (MAO), which destroys excess serotonin, so there is no point in increasing the rate if I do not inhibit this enzyme that destroys serotonin.

In Ayahuasca, along with DMT, there is a substance called harmaline that temporarily deactivates this enzyme (MAO). Basically, Ayahuasca fills your body with serotonin and doesn't let it out for at least two hours, this is how long it takes for this enzyme to be inhibited. The photosensitive scanner that is placed on top of the human being's head measures brain activity, if it is placed on Talita's head, I will notice that 10% of the areas of her brain are illuminated, this is her activity level. Now, if I put it in an hour or so, after the effects of the ayahuasca, I will be able to see 70% of the activity, an activity 7 times greater, a brain activity that you have never had before and you will see that it is completely different.

...You will notice a lot of things, not just defects, problems, errors. Ayahuasca reveals potential that you are unaware of, talents that you are unaware of and are not exploring. That's what it's for, on the one hand, it minimizes the things that get in the way of your life. On the other hand, it shows that we expect others and blame our frustrations. Sometimes what someone else does to me is no worse than what we do to ourselves. Thinking, hurting yourself, cultivating that energy. Ayahuasca works with character, improving us. Character is something that everyone says they have, the 'guy' could be in prison for 50 years and he'll say he has character. We justify many of our defects. The greatest compass for us to know how our character is, it is based on the things we need to do in secret, pay attention to this, the number of things we need to do in secret, shows that we are out of alignment with our truth. Character seems to be something good to be socially accepted. Character is good for one thing, so you don't suffer. When we have character, our life has quality, we move towards one thing. The freedom not to hide anything from anyone, not to be in public what you are hidden. And the freedom for me, [CENTER OWNER'S NAME REDACTED], to give my cell phone to my wife, that is freedom. For me, this is a positive thing. When we start to behave more honestly,

more decently, we gain quality of life. I talk a lot to boys, I work with men: 'Men, imagine that you have a serious relationship, when you are on the street with your wife, and a very attractive girl passes by on the other side, who attracts attention, if you have any sense, will you look? Of course not! And if she says the clothes are short, you still agree. Now, what if you are alone? If you don't do it in front of her, why do you do it hidden? This is about being honest, not with your wife, but with yourself.

I don't want to be the man who needs to hide in front of others. Not to brag, I have a lot to change. But for me, change comes when we move towards not wearing a mask, being a single person, a transparent person and not hiding anything from ourselves. It is not with [CENTER OWNER'S NAME REDACTED], my wife, but with my own conscience. Every day I ask myself, if I die today, with what face, will I return home, to the spiritual plane. I won't go back with shame because 15 years ago, I had the courage to live a different life than the one I lived before, to be a better person. Not for my mother to be proud of me, but for me to be proud of myself and live well. It's not about showing off to others, but about cultivating a more satisfying, fuller, healthier life. Much of what I'm talking about may sound subjective, puritanical, trippy, but in 4 hours you'll understand what I wanted to say. Ayahuasca proves itself over time."

B.3 Relation to Pre-Registration

We pre-registered the experiment in the AEA RCT Registry, with ID #10400, at https://www.socialscienceregistry.org/trials/10400. There are two key differences between the pre-registration and the current paper. First, in the pre-registration we describe two experiments: one in which the center assigned participants to a high or low dose of ayahuasca (diluted-dosage experiment), and a second in which the center assigned participants to a high dose of ayahuasca or a placebo, jurema. In this paper, we report the findings of the latter experiment. As we explain in the pre-registration, the purpose of the diluted-dosage experiment was to isolate the effects of ayahuasca, but there was a first stage problem: even those with the low dose often had meaningful trips. For example, 26% of the low-dose participants reported that their trip was the single most meaningful of their entire lives, and 38% reported having had visions. We successfully addressed this issue by moving to an experiment design with a non-ayahuasca placebo (jurema) group.

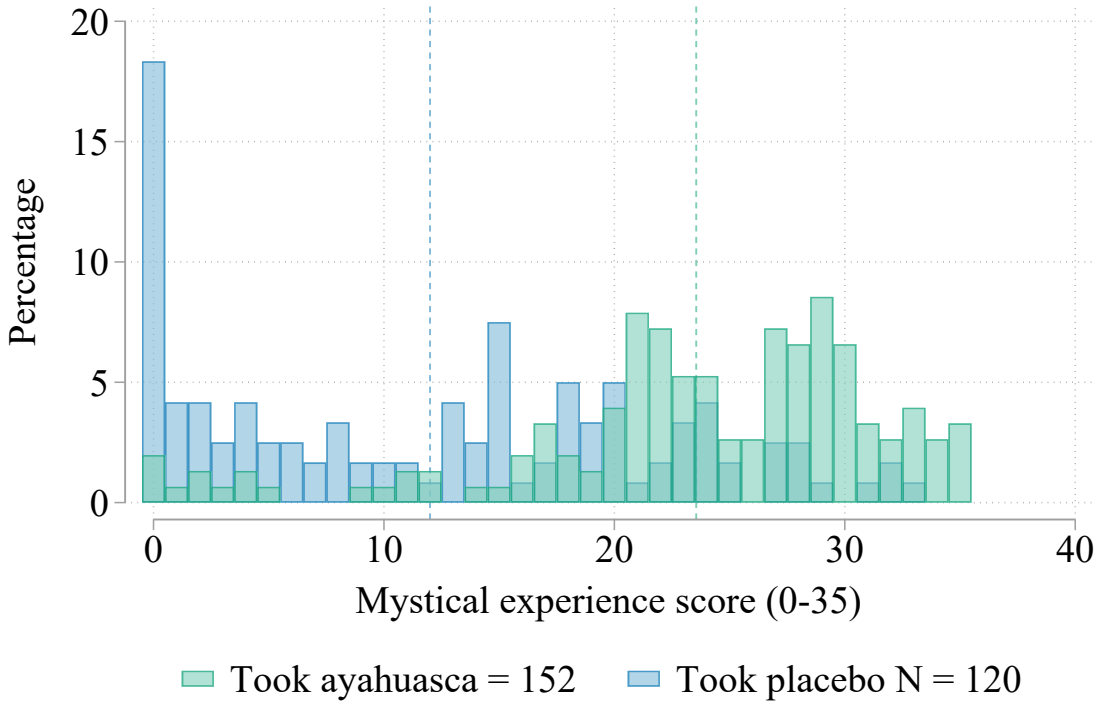
Second, we pre-registered both outcome measures related to well-being and a broader set related to decision-making and economic outcomes (e.g. employment status, savings, prosociality, etc.). In the current paper, we consider only the well-being outcomes—though we report these outcomes exhaustively. We are writing a separate paper on the effects on decision-making

and economic outcomes. In addition, while we mention that the topic of the lecture alternated between "happiness" and "taming the mind," we do not report the effects of the lecture variation on trips and treatment effects in this paper.

Otherwise, we had aimed to reach "ten or so sessions" with the jurema experiment design; but ultimately we only had funding to complete six sessions. Related, our goal was to reach 150-300 people in each of the two treatment arms: ayahuasca versus jurema. We came close to this target, with 126 receiving jurema and 159 receiving ayahuasca (or 126 receiving ayahuasca if we exclude the sixth session in which, by mistake, all participants were given ayahuasca).

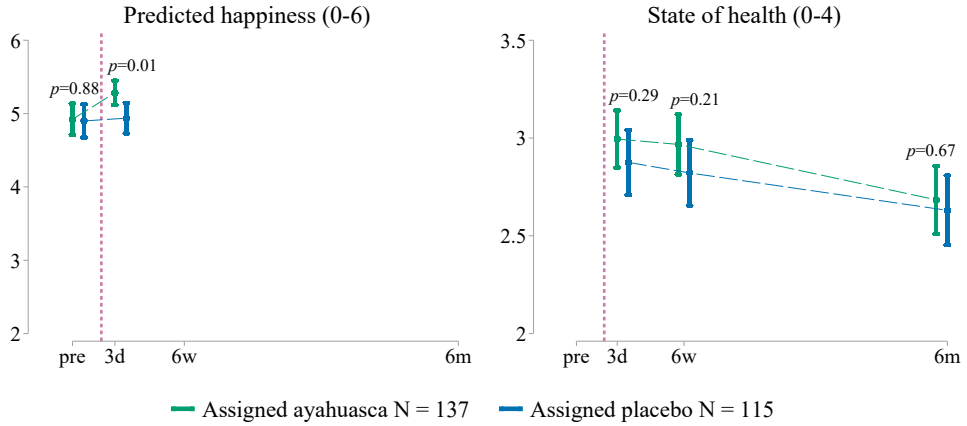
C Supplementary Figures

Fig. S1: Mystical experience scores by treatment group



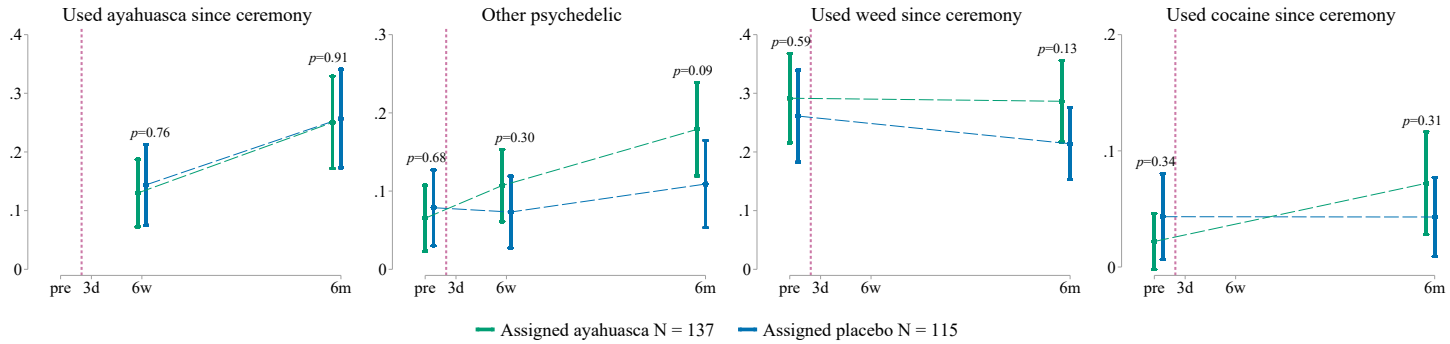
Note: Figure shows the histogram of mystical experience scores separately for those that took ayahuasca and those that took the placebo during the six experimental sessions.

Fig. S2: Effects of ayahuasca on predicted happiness and general health



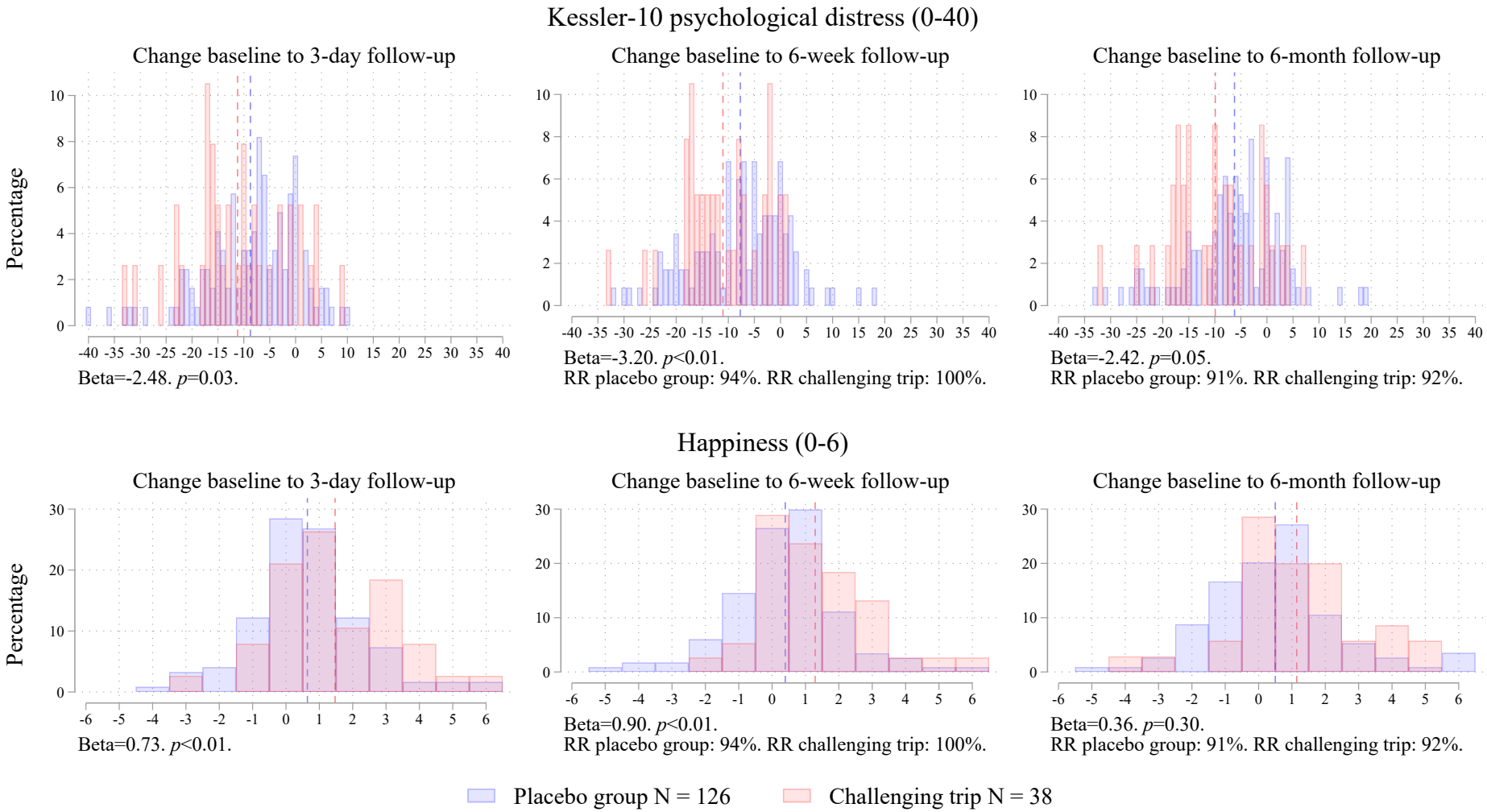
Note: Figure shows intent to treat effects. Baseline measures are denoted by pre and d/w/m denote days/weeks/months. First panel's outcome is the answer to the question *Now please predict how happy you will be in six weeks* on a scale from *Not very happy (0)* to *Very happy (6)*. Second panel's outcome is the answer to *All in all, how would you describe your state of health these days?* and choices go from *Very Poor (0)* to *Very Good (4)*. 95% confidence intervals are shown. *p*-values are from a regression that controls for the outcome at baseline where available (except for the baseline test), and session-by-gender fixed effects, with robust standard errors.

Fig. S3: Effects on subsequent drug use



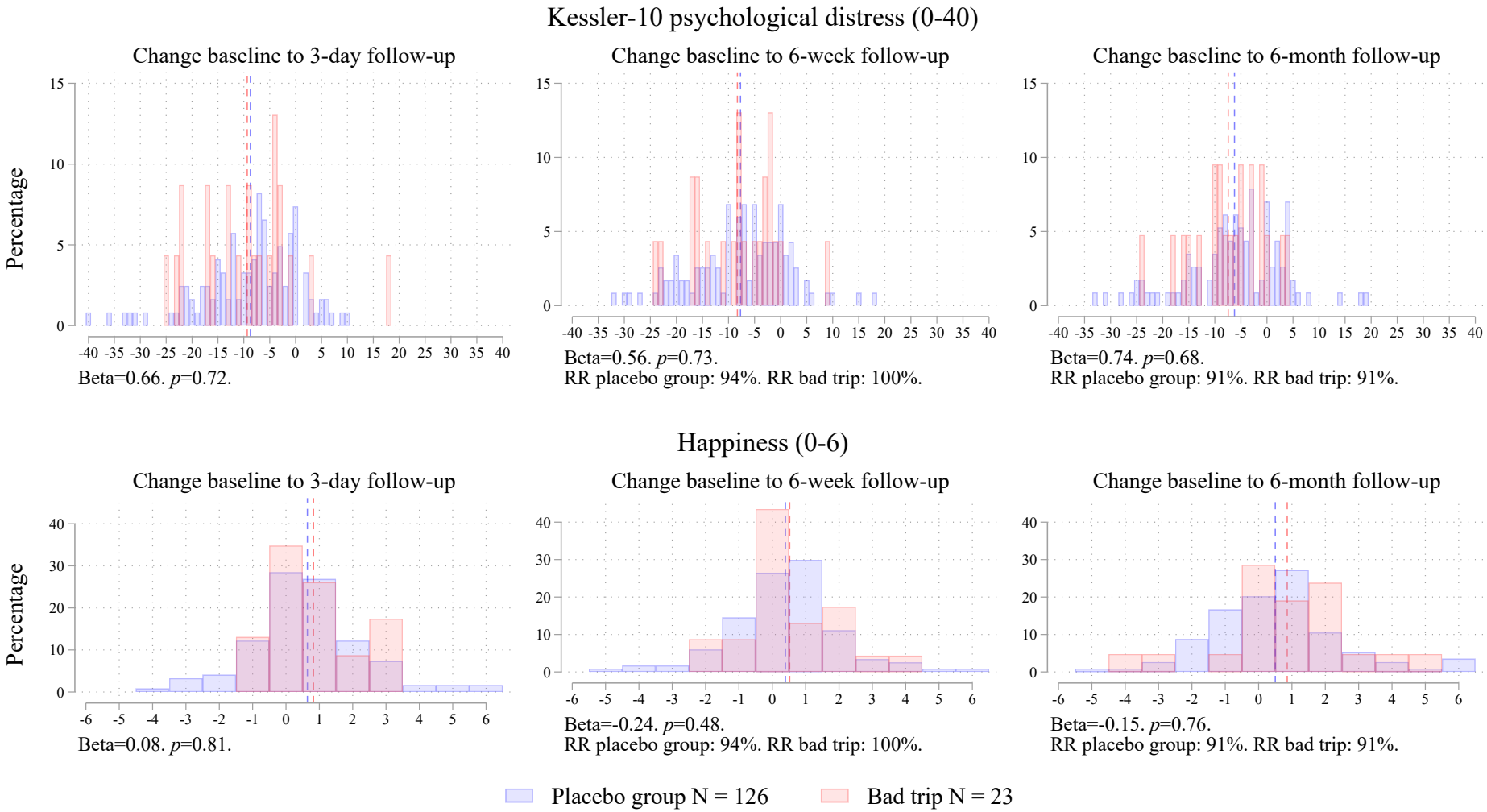
Note: Figure shows intent to treat effects. Baseline measures are denoted by pre, d/w/m denote days/weeks/months. Each panel shows effects of ayahuasca on binary outcomes: (i) whether the participant reports having taken ayahuasca since the ceremony, (ii) whether the participant reports taking psilocybin, LSD, or MDMA, (iii) whether the participant reports taking marijuana, and (iv) whether the participant reports taking cocaine. 95% confidence intervals are shown. *p*-values are from a regression that controls for the outcome at baseline when available (except for the baseline test) and session-by-gender fixed effects, with robust standard errors.

Fig. S4: Challenging trips improve well-being more than placebo



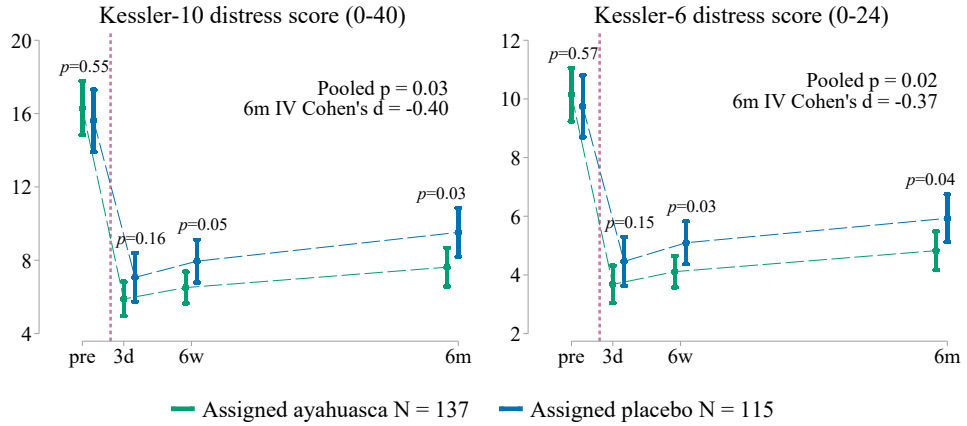
Note: The figure plots histograms of well-being changes for (i) participants that received ayahuasca and reported having a challenging trip, and (ii) participants that received the placebo. RR refers to response rate. Challenging trip participants have high response rates, limiting the possibility of negative effects obscured by non-response. Vertical dashed lines denote the mean well-being change for each group. The betas and *p*-values are obtained from a regression of the outcome on an indicator for receiving having had a challenging ayahuasca trip (the omitted group includes participants that received the placebo), controlling for the outcome at baseline, and session-by-gender fixed effects, with robust standard errors.

Fig. S5: Bad trips and placebo deliver similar changes in well-being



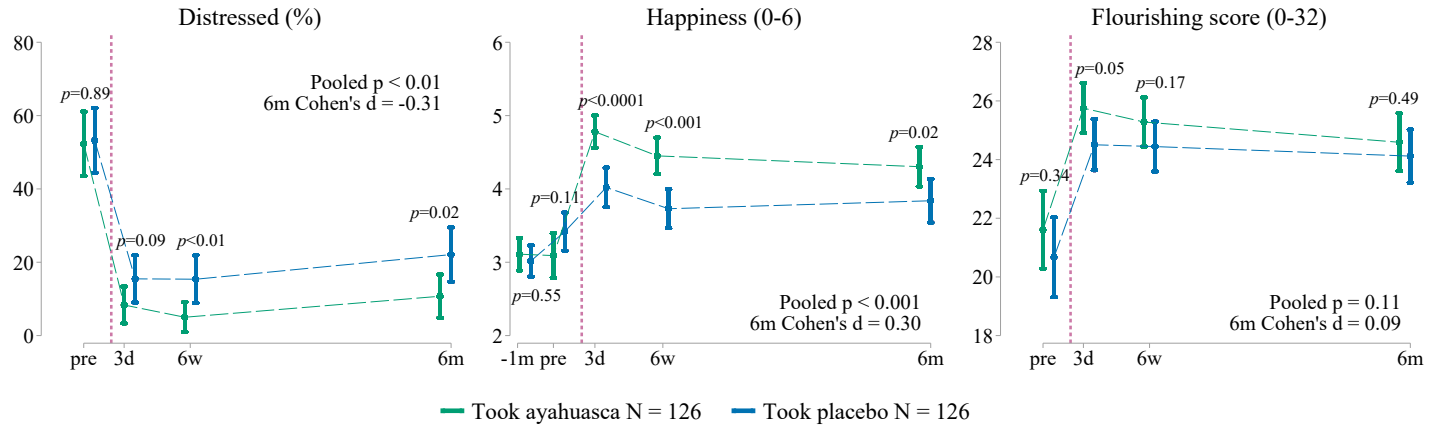
Note: The figure plots histograms of well-being changes for (i) participants that received ayahuasca and reported having a bad trip, and (ii) participants that received the placebo. RR refers to response rate. Bad trip participants have high response rates, limiting the possibility of negative effects obscured by non-response. Vertical dashed lines denote the mean well-being change for each group. The betas and *p*-values are obtained from a regression of the outcome on an indicator for receiving having had a challenging ayahuasca trip (the omitted group includes participants that received the placebo), controlling for the outcome at baseline, and session-by-gender fixed effects, with robust standard errors.

Fig. S6: Effects on psychological distress: robustness



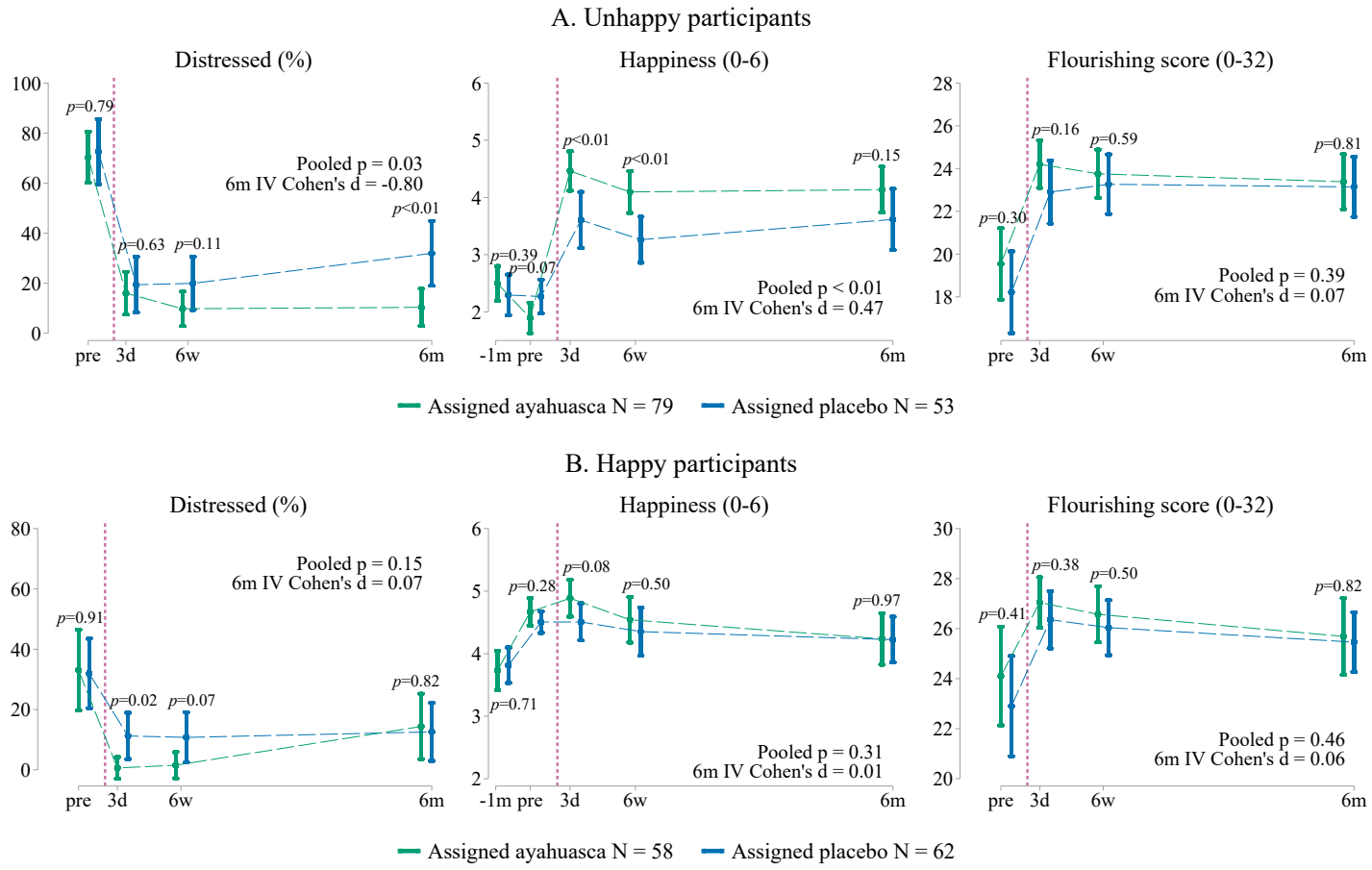
Note: Figure shows intent to treat effects. Baseline measures are denoted by pre, d/w/m denote days/weeks/months. Kessler-10 distress score is the 0 to 40 score on the Kessler-10 scale, while the Kessler-6 score is the score from the six-item version. 95% confidence intervals are shown. *p*-values are from a regression that controls for the outcome at baseline (except for the baseline and retrospective tests), and session-by-gender fixed effects, with robust standard errors. The pooled *p*-value is obtained from a regression pooling data from the three follow-up surveys. 6m IV Cohen's *d* is the standardized effect of ayahuasca at six months, when using treatment assigned as an instrumental variable for treatment received.

Fig. S7: Well-being effects using treatment actually received



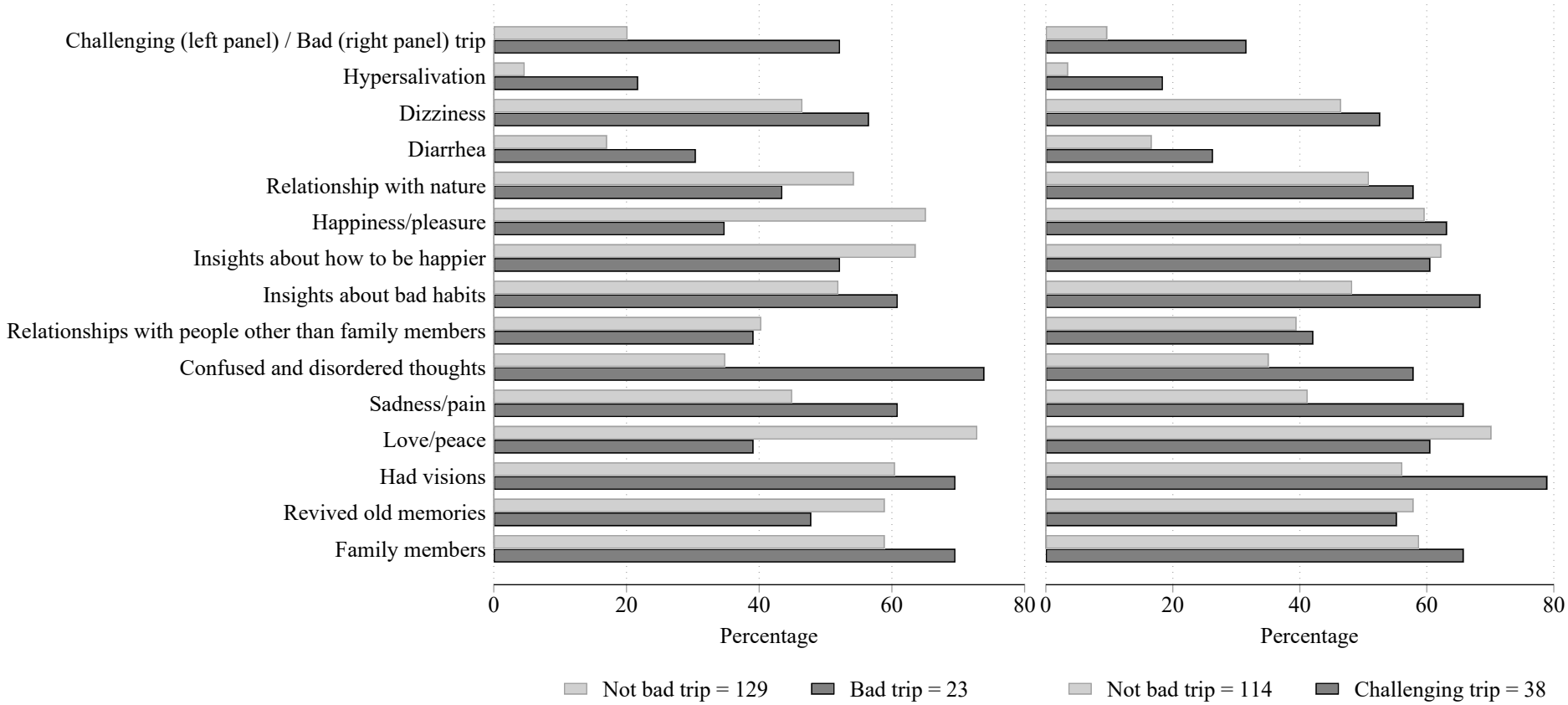
Note: Figure shows means by treatment actually received (as opposed to intent-to-treat estimates based on treatment assigned). Baseline measures are denoted by pre, -1m denotes a retrospective measure for the past month, d/w/m denote days/weeks/months. Distress (%) is the percentage of participants that score 15 or above on the Kessler psychological distress scale. Happiness is the answer to *In general, how happy would you say you are these days?* on a scale from *Not very happy (0)* to *Very happy (6)*. Flourishing is the score from 0 to 32 from summing answers to eight statements like *I lead a purposeful and meaningful life (0 = Strongly disagree to 4 = Strongly agree)*. 95% confidence intervals are shown. *p*-values are from a regression that controls for the outcome at baseline (except for the baseline and retrospective tests) and session-by-gender fixed effects, with robust standard errors. The pooled *p*-value is obtained from a regression pooling data from the three follow-up surveys. 6m Cohen's *d* is the standardized effect of ayahuasca at six months.

Fig. S8: Well-being effects are driven by unhappy participants



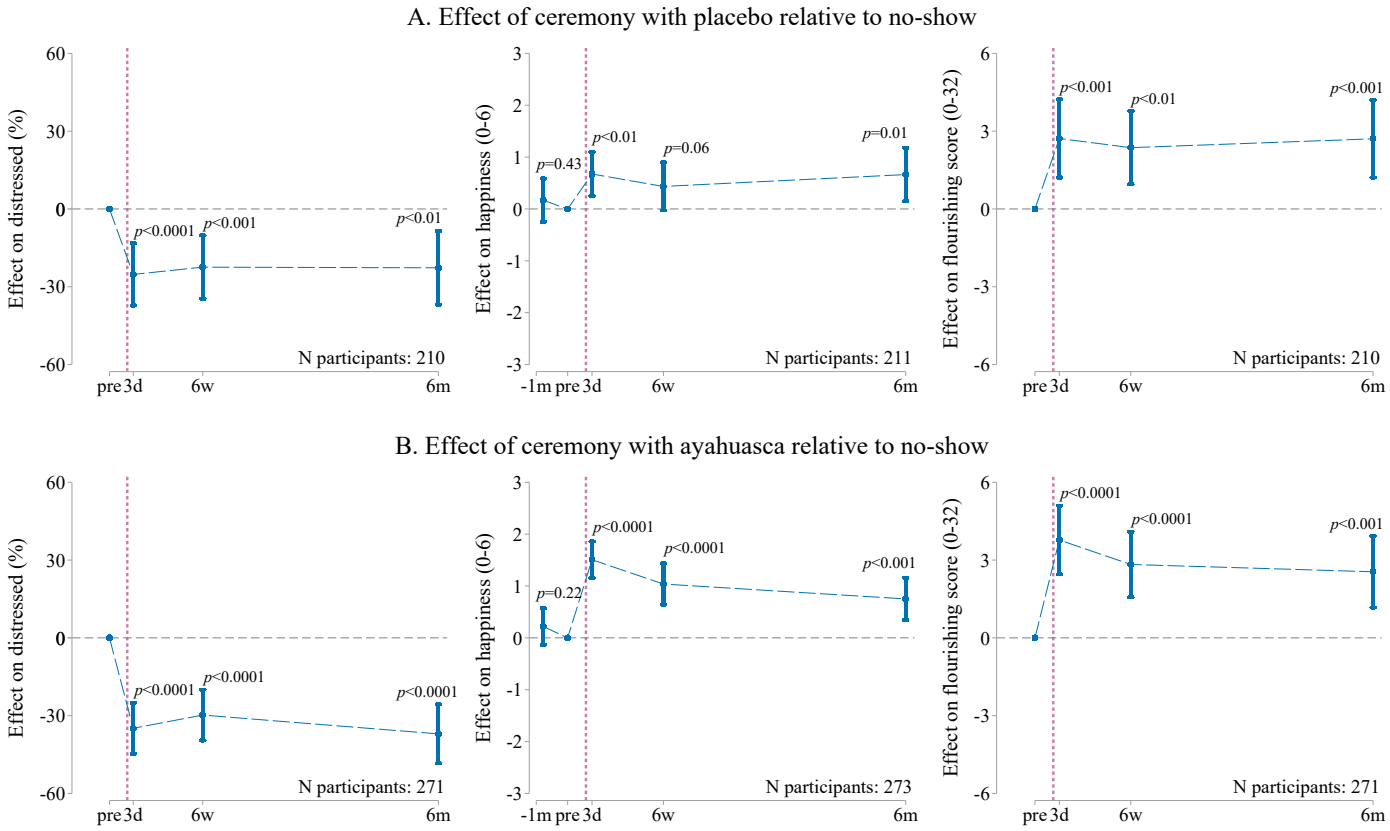
Note: Figure shows intent to treat effects. Baseline measures are denoted by pre, -1m denotes a retrospective measure for the past month. Distressed (%) is the percentage of participants that score 15 or above on the Kessler-10 Psychological Distress Scale. Happiness is the answer to *In general, how happy would you say you are these days?* on a scale from *Not very happy (0)* to *Very happy (6)*. Flourishing is the score from 0 to 32 from summing answers to eight statements like *I lead a purposeful and meaningful life (0 = Strongly disagree to 4 = Strongly agree)*. 95% confidence intervals are shown. p-values are from a regression that controls for the outcome at baseline (except for the baseline and retrospective comparisons) and session-by-gender fixed effects, with robust standard errors. The pooled p-value is obtained from a regression pooling data from the three follow-up surveys. 6m IV Cohen's d is the standardized effect of ayahuasca at six months, when using treatment assigned as an instrumental variable for treatment received. (**A**) presents results for the participants with below-median happiness at baseline ($0-3$), while (**B**) restricts to participants with above-median happiness at baseline ($3-6$).

Fig. S9: How do bad and challenging trips differ from other trips?



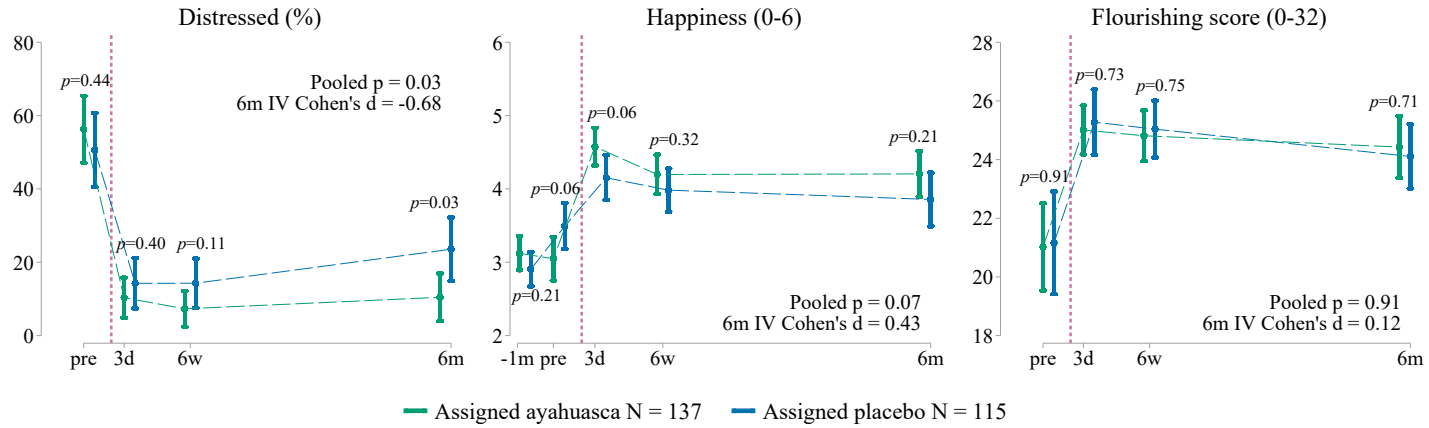
Note: Graph shows percentage of participants in each group that experienced each negative experience (bar pairs 1-4), or tripped on each broad domain (bar pairs 5-15) during the ceremony, as reported on the three-day follow-up survey. Sample includes all participants that received ayahuasca.

Fig. S10: Effects of ceremony controlling for baseline distress-specific time trends



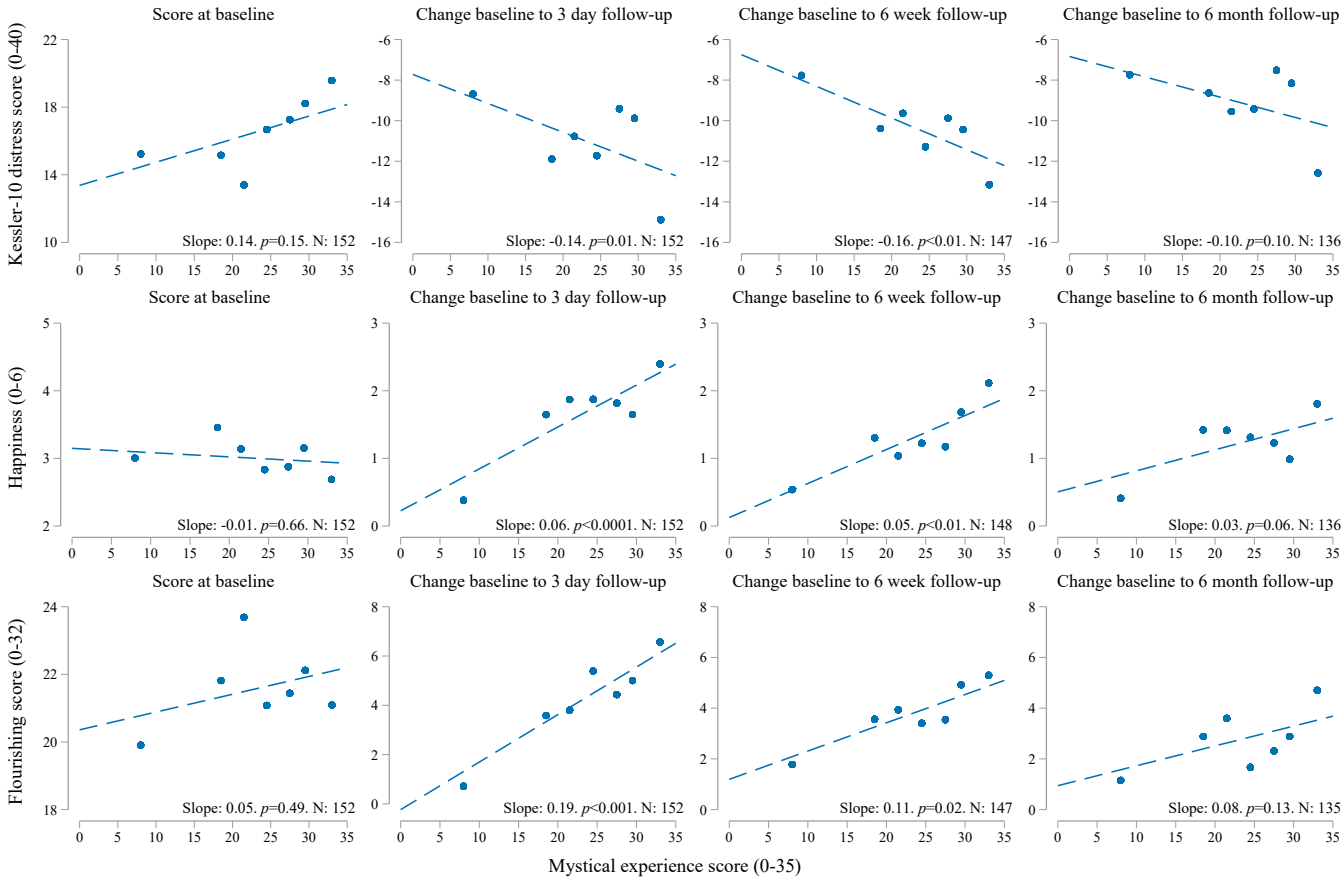
Note: Figure shows difference-in-differences effects of (**A**) attending the ceremony and taking the placebo relative to no-shows, and (**B**) attending the ceremony and taking ayahuasca relative to no-shows. The one difference from figure 4 is that each regression includes the baseline well-being measure interacted with dummy variables for each follow-up survey. 95% confidence intervals are shown, with standard errors clustered at participant-level.

Fig. S11: Well-being effects controlling for guessed treatment



Note: Figure shows intent to treat effects. Baseline measures are denoted by pre, -1m denotes a retrospective measure for the past month, d/w/m denote days/weeks/months. Distress (%) is the percentage of participants that score 15 or above on the Kessler Psychological Distress Scale. Happiness is the answer to *In general, how happy would you say you are these days?* on a scale from *Not very happy (0)* to *Very happy (6)*. Flourishing is the score from 0 to 32 from summing answers to eight statements like *I lead a purposeful and meaningful life (0 = Strongly disagree to 4 = Strongly agree)*. 95% confidence intervals are shown. *p*-values are from a regression that controls for the outcome at baseline (except for the baseline and retrospective tests), a dummy variable equal to one if the participant guessed that they received regular-concentration ayahuasca, and session-by-gender fixed effects, with robust standard errors. The pooled *p*-value is obtained from a regression pooling data from the three follow-up surveys. 6m IV Cohen's *d* is the standardized effect of ayahuasca at six months, when using treatment assigned as an instrumental variable for treatment received.

Fig. S12: More mystical trips predict greater improvements in well-being with guess control



Note: Each panel shows a binscatter plot correlating the mystical experience score (measured at the three-day follow-up) with baseline measures of well-being (first column), and changes in well-being from baseline to each of the follow-up surveys (second to fourth columns). Each panel controls for session-by-gender fixed effects, a dummy variable equal to one if the participant guessed that they received regular-concentration ayahuasca, and with the exception of column 1, the well-being outcome measured at baseline. Standard errors are robust.

D Supplementary Tables

Table S1: Characteristics of experimental participants

Variable:	N	Mean	St. dev	Min.	Pctl. 25	Median	Pctl. 75	Max.
(1) Age	426	34.72	9.92	18	27	33	42	66
(2) Female (0/1)	429	0.62	0.49	0	0	1	1	1
(3) Not white (0/1)	429	0.45	0.50	0	0	0	1	1
(4) Education (0-10)	429	5.70	1.68	1	4	6	7	9
(5) Married (0/1)	429	0.22	0.41	0	0	0	0	1
(6) Income (0-8)	429	2.77	1.48	0	2	3	4	7
(7) Has children (0/1)	429	0.49	0.50	0	0	0	1	1
(8) Employed (0/1)	429	0.81	0.39	0	1	1	1	1
(9) Employed in the formal sector (0/1)	429	0.42	0.49	0	0	0	1	1
(10) Drinks alcohol (0/1)	429	0.65	0.48	0	0	1	1	1
(11) Uses drugs (0/1)	429	0.31	0.46	0	0	0	1	1
(12) Practices a religion (0/1)	429	0.45	0.50	0	0	0	1	1
(13) Family history of alcoholism (0/1)	429	0.37	0.48	0	0	0	1	1
(14) Family history of depression (0/1)	429	0.44	0.50	0	0	0	1	1
(15) Family history of schizophrenia (0/1)	429	0.07	0.26	0	0	0	0	1
(16) Happiness (0-6)	429	3.03	1.67	0	2	3	4	6
(17) Predicted happiness (0-6)	429	4.79	1.44	0	4	5	6	6
(18) Depression last month (0-6)	429	2.69	1.99	0	1	3	4	6
(19) Happiness last month (0-6)	429	2.89	1.67	0	2	3	4	6
(20) K10 scale score (0-40)	429	17.24	9.30	0	10	17	25	40
(21) Meets moderate or severe psychological distress	429	0.58	0.49	0	0	1	1	1
(22) Flourishing score (0-32)	429	20.58	7.64	0	16	22	26	32
(23) Social desirability score (0-4)	429	2.10	0.82	0	2	2	3	4
(24) Work satisfaction (0-4)	349	2.32	1.07	0	1	3	3	4
(25) Cares what others think (0-4)	429	2.36	1.34	0	1	3	3	4

Notes: Table shows summary statistics from the baseline survey taken by the full set of 429 participants. For the outcome variable definitions that are not obvious, see Section A.3. Work satisfaction is only asked to participants that are employed.

Table S2: Balance on baseline characteristics: all participants

	Treatment assigned				Treatment received				Took the placebo (vs no-show)			
	Coef	SE	Control mean	N	Coef	SE	Control mean	N	Coef	SE	Control mean	N
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
Age	-1.91	(1.20)	35.05	251	-3.12**	(1.20)	35.64	251	0.71	(1.39)	34.97	238
Not white (0/1)	-0.02	(0.06)	0.47	252	0.00	(0.06)	0.46	252	-0.00	(0.07)	0.46	240
Education (0-10)	-0.00	(0.21)	5.79	252	-0.15	(0.20)	5.87	252	0.47**	(0.21)	5.44	240
Married (0/1)	-0.06	(0.05)	0.25	252	0.02	(0.05)	0.21	252	0.01	(0.05)	0.19	240
Income (0-8)	-0.01	(0.18)	2.81	252	0.01	(0.18)	2.81	252	0.23	(0.20)	2.61	240
Has children (0/1)	-0.04	(0.06)	0.49	252	-0.06	(0.06)	0.50	252	-0.02	(0.07)	0.52	240
Employed (0/1)	0.02	(0.05)	0.83	252	-0.01	(0.05)	0.85	252	0.10*	(0.05)	0.75	240
Employed in the formal sector (0/1)	0.00	(0.06)	0.42	252	-0.00	(0.06)	0.42	252	0.02	(0.07)	0.42	240
Drinks alcohol (0/1)	0.01	(0.06)	0.65	252	0.00	(0.06)	0.65	252	0.07	(0.06)	0.57	240
Uses drugs (0/1)	0.02	(0.06)	0.29	252	0.00	(0.06)	0.29	252	-0.07	(0.06)	0.38	240
Practices a religion (0/1)	0.00	(0.06)	0.41	252	-0.02	(0.06)	0.42	252	-0.06	(0.06)	0.48	240
Family history of alcoholism (0/1)	0.09	(0.06)	0.35	252	0.00	(0.06)	0.39	252	0.04	(0.06)	0.35	240
Family history of depression (0/1)	0.03	(0.06)	0.46	252	-0.02	(0.06)	0.48	252	0.13**	(0.06)	0.37	240
Family history of schizophrenia (0/1)	0.02	(0.03)	0.06	252	-0.04	(0.03)	0.09	252	0.02	(0.03)	0.06	240
Happiness (0-6)	-0.45**	(0.20)	3.50	252	-0.33	(0.20)	3.40	252	0.74***	(0.21)	2.63	240
Predicted happiness (0-6)	0.02	(0.16)	4.90	252	0.04	(0.16)	4.90	252	0.36*	(0.20)	4.45	240
Depression last month (0-6)	-0.11	(0.24)	2.57	252	-0.08	(0.24)	2.55	252	-0.48*	(0.27)	3.05	240
Happiness last month (0-6)	-0.17	(0.19)	3.16	252	-0.09	(0.19)	3.11	252	0.54**	(0.22)	2.54	240
K10 scale score (0-40)	0.69	(1.14)	15.57	252	-0.15	(1.14)	16.05	252	-3.69***	(1.18)	19.68	240
Meets moderate or severe psychological distress	0.06	(0.06)	0.50	252	-0.01	(0.06)	0.53	252	-0.18**	(0.06)	0.69	240
Flourishing score (0-32)	0.38	(0.98)	20.94	252	0.93	(0.96)	20.69	252	1.70	(1.02)	18.86	240
Social desirability score (0-4)	-0.07	(0.10)	2.12	252	0.11	(0.10)	2.03	252	-0.05	(0.11)	2.08	240
Work satisfaction (0-4)	-0.03	(0.15)	2.40	213	0.02	(0.15)	2.37	213	0.07	(0.16)	2.29	192
Cares what others think (0-4)	0.31*	(0.17)	2.26	252	0.06	(0.17)	2.40	252	0.14	(0.19)	2.24	240
Pooled F-test p-value			0.33				0.42				<0.01	

Notes: The table excludes participants assigned to the all-treated session. Treatment assigned columns compare participants who attended their session and were randomly assigned to receive ayahausca versus the placebo (control mean is for the placebo group). Treatment received columns compare participants who attended their session and actually received ayahuasca with those that attended and actually received the placebo. Took the placebo vs no-show columns compare participants who attended their session and actually received the placebo to those that did not attend their session. Each coefficient and standard error is obtained from a regression of the covariate (listed in the far-left column) on a dummy for the comparison of interest, controlling for session-by-gender (randomization strata) fixed effects. Standard errors are robust. The pooled F-test p-value corresponds to the p-value from a test of joint significance for all the covariates in the table. *** p<0.01, ** p<0.05, * p<0.1.

Table S3: Balance on baseline characteristics: responded to three-day follow-up

	Treatment assigned				Treatment received				Took the placebo (vs no-show)			
	Coef	SE	Control mean	N	Coef	SE	Control mean	N	Coef	SE	Control mean	N
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
Age	-1.87	(1.21)	35.00	244	-3.08**	(1.22)	35.58	244	0.86	(1.53)	34.54	204
Not white (0/1)	-0.01	(0.07)	0.47	245	-0.00	(0.06)	0.46	245	0.01	(0.07)	0.45	206
Education (0-10)	-0.02	(0.21)	5.83	245	-0.16	(0.21)	5.89	245	0.51**	(0.23)	5.40	206
Married (0/1)	-0.06	(0.05)	0.25	245	0.01	(0.05)	0.22	245	-0.04	(0.06)	0.23	206
Income (0-8)	-0.00	(0.19)	2.81	245	0.03	(0.18)	2.80	245	0.22	(0.22)	2.61	206
Has children (0/1)	-0.02	(0.06)	0.48	245	-0.07	(0.06)	0.50	245	-0.05	(0.07)	0.54	206
Employed (0/1)	0.01	(0.05)	0.85	245	-0.01	(0.05)	0.85	245	0.12**	(0.06)	0.73	206
Employed in the formal sector (0/1)	0.00	(0.06)	0.42	245	-0.01	(0.06)	0.42	245	0.01	(0.07)	0.42	206
Drinks alcohol (0/1)	0.02	(0.06)	0.64	245	-0.00	(0.06)	0.64	245	0.06	(0.07)	0.58	206
Uses drugs (0/1)	0.01	(0.06)	0.29	245	-0.03	(0.06)	0.30	245	-0.09	(0.07)	0.40	206
Practices a religion (0/1)	0.01	(0.06)	0.41	245	0.00	(0.06)	0.41	245	-0.11	(0.07)	0.49	206
Family history of alcoholism (0/1)	0.08	(0.06)	0.35	245	0.01	(0.06)	0.39	245	0.05	(0.07)	0.35	206
Family history of depression (0/1)	0.03	(0.06)	0.46	245	-0.02	(0.06)	0.49	245	0.13*	(0.07)	0.37	206
Family history of schizophrenia (0/1)	0.01	(0.03)	0.06	245	-0.04	(0.03)	0.09	245	0.03	(0.04)	0.06	206
Happiness (0-6)	-0.45**	(0.20)	3.53	245	-0.28	(0.20)	3.41	245	0.72***	(0.24)	2.67	206
Predicted happiness (0-6)	0.08	(0.16)	4.87	245	0.08	(0.16)	4.87	245	0.29	(0.23)	4.48	206
Depression last month (0-6)	-0.17	(0.25)	2.63	245	-0.08	(0.24)	2.58	245	-0.59*	(0.30)	3.17	206
Happiness last month (0-6)	-0.11	(0.19)	3.12	245	-0.08	(0.19)	3.10	245	0.56**	(0.24)	2.53	206
K10 scale score (0-40)	0.65	(1.16)	15.72	245	-0.11	(1.15)	16.18	245	-3.37**	(1.35)	19.61	206
Meets moderate or severe psychological distress	0.06	(0.06)	0.50	245	-0.00	(0.06)	0.54	245	-0.14*	(0.07)	0.66	206
Flourishing score (0-32)	0.62	(0.99)	20.75	245	1.09	(0.97)	20.55	245	0.95	(1.15)	19.36	206
Social desirability score (0-4)	-0.06	(0.11)	2.12	245	0.10	(0.11)	2.04	245	-0.14	(0.13)	2.16	206
Work satisfaction (0-4)	-0.04	(0.16)	2.41	208	-0.01	(0.15)	2.39	208	0.00	(0.17)	2.34	166
Cares what others think (0-4)	0.26	(0.17)	2.31	245	0.04	(0.17)	2.43	245	0.25	(0.21)	2.18	206
Pooled F-test p-value		0.21				0.52				<0.01		

Notes: The table is identical to the first baseline balance table, with the exception that it restricts to participants that responded to the three-day follow-up survey.

Table S4: Balance on baseline characteristics: responded to six-week follow-up

	Treatment assigned				Treatment received				Took the placebo (vs no-show)			
	Coef	SE	Control mean	N	Coef	SE	Control mean	N	Coef	SE	Control mean	N
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
Age	-1.77	(1.23)	35.08	238	-2.85**	(1.23)	35.59	238	1.31	(1.59)	34.27	195
Not white (0/1)	-0.01	(0.07)	0.47	239	-0.01	(0.07)	0.47	239	0.04	(0.07)	0.42	197
Education (0-10)	-0.08	(0.21)	5.90	239	-0.20	(0.21)	5.96	239	0.55**	(0.23)	5.44	197
Married (0/1)	-0.06	(0.06)	0.25	239	0.02	(0.05)	0.21	239	-0.06	(0.06)	0.25	197
Income (0-8)	-0.07	(0.18)	2.84	239	0.05	(0.18)	2.79	239	0.35	(0.22)	2.49	197
Has children (0/1)	-0.02	(0.07)	0.48	239	-0.04	(0.07)	0.49	239	-0.01	(0.07)	0.49	197
Employed (0/1)	0.00	(0.05)	0.85	239	-0.01	(0.05)	0.86	239	0.13**	(0.06)	0.73	197
Employed in the formal sector (0/1)	-0.03	(0.06)	0.43	239	-0.01	(0.06)	0.42	239	0.03	(0.07)	0.41	197
Drinks alcohol (0/1)	-0.00	(0.06)	0.65	239	0.01	(0.06)	0.64	239	0.11	(0.07)	0.53	197
Uses drugs (0/1)	0.02	(0.06)	0.27	239	-0.03	(0.06)	0.30	239	-0.05	(0.07)	0.37	197
Practices a religion (0/1)	0.01	(0.06)	0.41	239	-0.01	(0.06)	0.42	239	-0.10	(0.07)	0.49	197
Family history of alcoholism (0/1)	0.06	(0.06)	0.36	239	-0.01	(0.06)	0.39	239	0.02	(0.07)	0.38	197
Family history of depression (0/1)	0.02	(0.07)	0.45	239	-0.04	(0.06)	0.48	239	0.10	(0.07)	0.39	197
Family history of schizophrenia (0/1)	0.00	(0.03)	0.07	239	-0.05*	(0.03)	0.09	239	0.01	(0.04)	0.08	197
Happiness (0-6)	-0.43**	(0.20)	3.46	239	-0.34*	(0.20)	3.38	239	0.72***	(0.23)	2.66	197
Predicted happiness (0-6)	0.06	(0.16)	4.87	239	0.10	(0.16)	4.85	239	0.30	(0.22)	4.43	197
Depression last month (0-6)	-0.20	(0.25)	2.64	239	-0.18	(0.25)	2.63	239	-0.63**	(0.30)	3.25	197
Happiness last month (0-6)	-0.08	(0.19)	3.08	239	0.01	(0.19)	3.03	239	0.56**	(0.23)	2.46	197
K10 scale score (0-40)	0.53	(1.18)	15.71	239	-0.21	(1.16)	16.14	239	-3.50**	(1.36)	19.70	197
Meets moderate or severe psychological distress	0.06	(0.07)	0.49	239	-0.02	(0.07)	0.53	239	-0.15**	(0.07)	0.67	197
Flourishing score (0-32)	0.15	(0.99)	20.98	239	0.57	(0.98)	20.81	239	1.49	(1.15)	19.20	197
Social desirability score (0-4)	-0.07	(0.11)	2.10	239	0.12	(0.11)	2.01	239	-0.21*	(0.12)	2.20	197
Work satisfaction (0-4)	-0.06	(0.15)	2.43	203	-0.07	(0.15)	2.44	203	0.06	(0.16)	2.34	159
Cares what others think (0-4)	0.26	(0.17)	2.34	239	0.05	(0.17)	2.46	239	0.16	(0.21)	2.28	197
Pooled F-test p-value		0.47				0.14				<0.01		

Notes: The table is identical to the first baseline balance table, with the exception that it restricts to participants that responded to the six-week follow-up survey.

Table S5: Balance on baseline characteristics: responded to six-month follow-up

	Treatment assigned				Treatment received				Took the placebo (vs no-show)			
	Coef	SE	Control mean	N	Coef	SE	Control mean	N	Coef	SE	Control mean	N
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
Age	-2.03	(1.30)	35.32	224	-3.13**	(1.31)	35.83	224	0.77	(1.57)	35.00	190
Not white (0/1)	-0.02	(0.07)	0.47	225	0.00	(0.07)	0.46	225	-0.00	(0.08)	0.46	191
Education (0-10)	-0.05	(0.22)	5.86	225	-0.17	(0.22)	5.91	225	0.50**	(0.24)	5.42	191
Married (0/1)	-0.05	(0.06)	0.26	225	0.05	(0.06)	0.21	225	-0.06	(0.06)	0.25	191
Income (0-8)	0.02	(0.19)	2.85	225	0.07	(0.19)	2.83	225	0.32	(0.23)	2.53	191
Has children (0/1)	-0.03	(0.07)	0.48	225	-0.04	(0.07)	0.49	225	-0.04	(0.08)	0.53	191
Employed (0/1)	0.01	(0.05)	0.86	225	-0.04	(0.05)	0.88	225	0.16**	(0.06)	0.72	191
Employed in the formal sector (0/1)	0.02	(0.07)	0.42	225	-0.01	(0.07)	0.43	225	0.05	(0.07)	0.41	191
Drinks alcohol (0/1)	0.01	(0.06)	0.65	225	0.04	(0.06)	0.63	225	0.08	(0.07)	0.55	191
Uses drugs (0/1)	-0.03	(0.06)	0.30	225	-0.03	(0.06)	0.30	225	-0.04	(0.07)	0.34	191
Practices a religion (0/1)	-0.01	(0.07)	0.43	225	-0.02	(0.07)	0.43	225	-0.11	(0.07)	0.53	191
Family history of alcoholism (0/1)	0.05	(0.07)	0.37	225	-0.00	(0.07)	0.39	225	0.04	(0.07)	0.37	191
Family history of depression (0/1)	0.00	(0.07)	0.48	225	-0.04	(0.07)	0.50	225	0.12	(0.07)	0.41	191
Family history of schizophrenia (0/1)	0.01	(0.04)	0.07	225	-0.05	(0.03)	0.10	225	0.04	(0.04)	0.05	191
Happiness (0-6)	-0.48**	(0.20)	3.46	225	-0.40*	(0.21)	3.37	225	0.68**	(0.25)	2.63	191
Predicted happiness (0-6)	0.07	(0.16)	4.85	225	0.08	(0.17)	4.83	225	0.20	(0.23)	4.54	191
Depression last month (0-6)	-0.15	(0.26)	2.56	225	-0.17	(0.25)	2.57	225	-0.56*	(0.31)	3.17	191
Happiness last month (0-6)	-0.07	(0.20)	3.16	225	-0.02	(0.20)	3.13	225	0.55**	(0.25)	2.51	191
K10 scale score (0-40)	0.73	(1.20)	15.59	225	0.30	(1.19)	15.91	225	-3.87**	(1.40)	20.07	191
Meets moderate or severe psychological distress	0.06	(0.07)	0.49	225	0.01	(0.07)	0.52	225	-0.17**	(0.07)	0.68	191
Flourishing score (0-32)	0.61	(1.00)	20.88	225	0.57	(1.01)	20.93	225	1.35	(1.18)	19.25	191
Social desirability score (0-4)	-0.09	(0.11)	2.13	225	0.11	(0.11)	2.03	225	-0.10	(0.13)	2.09	191
Work satisfaction (0-4)	-0.04	(0.16)	2.38	193	-0.10	(0.16)	2.40	193	-0.00	(0.17)	2.35	156
Cares what others think (0-4)	0.28	(0.18)	2.30	225	0.08	(0.18)	2.41	225	0.15	(0.22)	2.24	191
Pooled F-test p-value		0.27				0.07				<0.01		

Notes: The table is identical to the first baseline balance table, with the exception that it restricts to participants that responded to the six-month follow-up survey.

Table S6: Effect of ayahuasca on ceremony experience

	Meaningful score (1)	Mystical experience (2)	Ego dissolution (3)	Word count (4)	N trip domains (5)	Had visions (6)
Received ayahuasca	2.36***	11.81***	51.37***	37.50**	3.14***	0.53***
	(0.36)	(1.58)	(10.85)	(14.94)	(0.46)	(0.07)
Placebo group outcome mean	3.4	12.0	245.4	63.6	3.5	0.1
Placebo group outcome SD	2.5	9.8	58.0	66.8	2.4	0.3
Observations	241	240	240	240	241	241
Session-by-gender fixed effects	Yes	Yes	Yes	Yes	Yes	Yes

Notes: Table shows regressions results from an IV specification, where treatment assigned serves as an instrument for actual treatment received. Sample includes participants that attended their assigned session, but excludes the session in which all participants were erroneously given ayahuasca. Placebo group refers to the participants that received the placebo. All outcomes are measured in the three-day follow-up survey. Meaningful score corresponds to the question *How personally meaningful was the experience?* on a scale from 0 to 7. Mystical experience corresponds to the 0-35 score on the mystical experience questionnaire, where participants rate seven items on a scale from 0 to 5 according to the degree to which they experience phenomena like *Sense of awe or awesomeness*. Ego dissolution corresponds to the 0-500 score after summing responses on a scale from 0 to 100 to five statements such as *I felt a sense of union with others*. Word count is the total number of words in the participant's open response to the question *Describe in detail your experience with the Ayahuasca in the box below. Please be specific about what you saw, heard, and felt.* N Trip Domains is the total number of domains, such as *Revived old memories* and *Love or Peace*, that the participant "tripped on". Had visions indicates whether the participant reported having visions during the ceremony. For detailed outcome variable definitions, see Section A.3. The first stage coefficient is 0.73 (i.e. being randomly assigned ayahuasca increases the probability of actually receiving ayahuasca by 73 percentage points). *** p<0.01, ** p<0.05, * p<0.1.

Table S7: Effect of ayahuasca on negative aspects of ceremony experience

	Vomit (1)	Diarrhea (2)	Dizziness (3)	Bad (4)	Challenging (5)	Hyper-salivation (6)	Other (7)	N neg effects (8)
Received ayahuasca	0.62***	0.11**	0.27***	0.10**	0.19***	0.04	0.02	1.35***
	(0.06)	(0.05)	(0.07)	(0.05)	(0.06)	(0.04)	(0.07)	(0.18)
Placebo group outcome mean	0.05	0.04	0.09	0.03	0.05	0.05	0.21	0.52
Placebo group outcome SD	0.22	0.20	0.29	0.16	0.22	0.22	0.41	0.77
Observations	240	240	240	240	240	240	240	240
Session-by-gender fixed effects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Notes: Table shows regressions results from an IV specification, where treatment assigned serves as an instrument for actual treatment received. Sample includes participants that attended their assigned session, but excludes the session in which all participants were erroneously given ayahuasca. Placebo group refers to the participants that received the placebo. All outcomes are measured in the three-day follow-up survey. Outcomes in columns (1)-(7) correspond to checkboxes selected for the question *We know that some people can have negative effects during an ayahuasca session. Did any of the following happen during your trip? Please select all that apply.* N neg effects is the sum of negative effects selected, from 0 to 7. For detailed outcome variable definitions, see Section A.3. The first stage coefficient is 0.73 (i.e. being randomly assigned ayahuasca increases the probability of actually receiving ayahuasca by 73 percentage points). *** p<0.01, ** p<0.05, * p<0.1.

Table S8: Little evidence of negative side effects of ayahuasca

	Increased heart rate	Increased blood pressure	Chest pain or tightness	Agitation	Dizziness	Confusion	Headaches	Visual disturbances	Paranoid thoughts and behaviors	Mood disturbances	Other	Total symptoms
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
Assigned ayahuasca	2.70	-6.66*	5.82	5.44	-2.16	0.25	-5.63	4.04	-2.40	1.37	5.31	0.08
	(2.72)	(3.42)	(4.27)	(5.92)	(3.81)	(4.11)	(6.23)	(3.30)	(4.18)	(6.33)	(4.78)	(0.23)
Placebo group outcome mean	2.9	10.7	8.7	22.3	9.7	9.7	35.9	4.9	11.7	32.0	13.6	1.6
Observations	223	223	223	223	223	223	223	223	223	223	223	223
Session-by-gender fixed effects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Notes: Table shows intent-to-treat effects from a regression of each health symptom on an indicator equal to one for participants assigned ayahausca, and zero for those assigned the placebo (jurema). At six-month follow-up, participants were asked *Do you experience any of the following? Check all that apply* with checkboxes for each of the symptoms above. *Total Symptoms* is the sum of symptoms checked (0-11). Sample includes participants that came to their session, and excludes the all-treated session. Robust standard errors in parentheses. *** p<0.01, ** p<0.05, * p<0.1.

Table S9: Trip intensity predicts well-being changes

	Baseline			Change baseline to 3-day			Change baseline to 6-week			Change baseline to 6-month		
	MN	ME	ED	MN	ME	ED	MN	ME	ED	MN	ME	ED
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
Outcome: K10	1.92	1.38	0.62	-2.14**	-1.57**	-1.43***	-2.23*	-1.70***	-1.18**	-0.23	-0.86	-0.67
	(1.74)	(.96)	(.78)	(.91)	(.56)	(.45)	(1.32)	(.57)	(.44)	(1.11)	(.59)	(.49)
Outcome mean	16.5	16.6	16.6	-11.0	-11.1	-11.1	-10.3	-10.4	-10.4	-9.1	-9.2	-9.2
N	153	152	152	153	152	152	148	147	147	137	136	136
Session-by-gender fixed effects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome: Happiness	-0.14	-0.06	-0.06	0.92***	0.62***	0.37***	0.55*	0.55***	0.23*	-0.02	0.27*	0.13
	(.3)	(.15)	(.15)	(.25)	(.12)	(.13)	(.29)	(.17)	(.13)	(.23)	(.16)	(.13)
Outcome mean	3.0	3.0	3.0	1.7	1.7	1.7	1.3	1.3	1.3	1.2	1.2	1.2
N	153	152	152	153	152	152	149	148	148	137	136	136
Session-by-gender fixed effects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome: Flourishing score	0.51	0.53	0.44	2.63**	1.94***	1.34***	2.17***	1.04**	0.72*	-0.46	0.65	0.72
	(1.09)	(.77)	(.56)	(1.18)	(.51)	(.39)	(.71)	(.48)	(.37)	(.94)	(.52)	(.46)
Outcome mean	21.7	21.6	21.6	4.3	4.3	4.3	3.8	3.8	3.8	2.8	2.8	2.8
N	153	152	152	153	152	152	148	147	147	136	135	135
Session-by-gender fixed effects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Notes: Sample includes all participants that received ayahuasca. MN is Meaningfulness, ED is Ego dissolution, and ME is Mystical experience. Table shows the results of regressing the well-being measure (either baseline or change from baseline to follow-up) on either MN, ED, or ME (each of these variables is standardized), controlling for session-by-gender fixed effects, and in the case of columns 4 to 12, controlling also for the well-being measure at baseline. K10 corresponds to the score, from 0 to 40, on the Kessler-10 distress scale, where participants rate how often they have felt things such as *tired out for no good reason* over the past 3 days. Happiness corresponds to the answer to *In general, how happy would you say you are these days?* on a scale from *Not very happy (0)* to *Very happy (6)*. Flourishing is the score from 0 to 32 from summing answers to eight statements like *I lead a purposeful and meaningful life (0 = Strongly disagree to 4 = Strongly agree)*. Meaningful score corresponds to answer to question *How personally meaningful was the experience?* on a scale from 0 to 7. Mystical experience corresponds to the score (from 0 to 35) on the mystical experience questionnaire, where participants rate on a scale from 0 to 5 the degree to which they experienced phenomena like *Sense of awe or awesomeness* during the ceremony. Ego dissolution corresponds to the score (from 0 to 500) obtained from adding the participant's responses to 5 statements where they rate (on a scale from 0 to 100) the extent to which they experienced things such as *I felt a sense of union with others* during the ceremony. All these outcomes were measured on the three-day follow-up. For detailed outcome variable definitions, see Section A.3. Robust standard errors in parentheses. *** p<0.01, ** p<0.05, * p<0.1.

Table S10: Well-being effects are not driven by participants that give socially desirable answers at baseline

	Distressed			Happiness			Flourishing score		
	3d	6w	6m	3d	6w	6m	3d	6w	6m
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Assigned ayahuasca × Social desirability ≤ Median	-0.06	-0.11**	-0.11*	0.71***	0.69***	0.47*	0.82	0.81	0.13
	(0.05)	(0.05)	(0.06)	(0.22)	(0.21)	(0.25)	(0.72)	(0.70)	(0.86)
Assigned ayahuasca × Social desirability > Median	-0.04	-0.05	-0.15	0.57*	0.15	0.29	-0.20	-1.75	0.52
	(0.07)	(0.08)	(0.09)	(0.34)	(0.38)	(0.41)	(1.27)	(1.12)	(1.10)
p-value for the difference	0.80	0.51	0.71	0.74	0.23	0.72	0.48	0.05	0.79
Outcome mean	0.12	0.10	0.17	4.40	4.10	4.07	25.13	24.87	24.35
Observations	243	237	224	244	238	224	243	235	221
Session-by-gender fixed effects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Notes: 3d, 6w, and 6m refer to the outcome being measured in the 3-day, 6-week, and 6-month follow-up surveys. Sample includes participants that attended their assigned session, except the all-treated session. Social desirability score is a measure of a participant's tendency to give socially desirable answers, measured with true/false answers to statements like, *No matter who I'm talking to, I'm always a good listener*. For this statement, an answer of true is considered to be the socially desirable (and likely false) answer. For more details, see Section A.3. The table shows intent-to-treat effects of ayahuasca, separately for those that have a social desirability score above or weakly below the median. All specifications control for the outcome measure at baseline and an indicator for social desirability score below median. Robust standard errors in parentheses. *** p<0.01, ** p<0.05, * p<0.1.

Table S11: Difference-in-differences effects of believing you received ayahuasca

	Distressed (1)	Happiness (2)	Flourishing (3)	Distressed (4)	Happiness (5)	Flourishing (6)
Believe took ayahuasca	-9.57	0.52*	-0.10			
	(6.12)	(0.30)	(0.70)			
Believe took ayahuasca (t+1)				0.08	-0.12	0.67
				(5.75)	(0.25)	(0.63)
Observations	486	488	478	524	526	520
Participants	243	244	239	262	263	260
Outcome mean	13.4	4.0	24.7	11.3	4.2	25.1
Participant fixed effects	Yes	Yes	Yes	Yes	Yes	Yes
Session-by-gender-by-follow-up fixed effects	Yes	Yes	Yes	Yes	Yes	Yes

Notes: The unit of observation is the participant-by-follow-up survey. Regressions include all participants that attended their assigned ceremony. Distressed is equal to 100 if the participant scores 15 or more on the Kessler-10 psychological distress index, and zero otherwise. Happiness ranges from 0 (Not very happy) to 6 (Very happy). Flourishing is the score on the Flourishing scale from 0 to 32. Columns 1 to 3 keep only the six-week and six-month follow-up surveys. Columns 4 to 6 keep only the three-day and six-week follow-up surveys. Believe took ayahuasca is a dummy variable equal to one if the participant believes they were given ayahuasca in their assigned ceremony. For the six-week follow-up, this belief variable is determined by the participant's guess of their treatment in the three-day follow-up. Since treatment is revealed at the end of the six-week follow-up survey, the belief variable is set to the truth for the six-month follow-up. Believe took ayahuasca (t+1) is the lead (as opposed to the lag) of the believe took ayahuasca variable. It follows that columns 4 to 6 serve as a placebo, or parallel pre-trends, check. Standard errors are clustered at the participant-level. *** p<0.01, ** p<0.05, * p<0.1.